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ULTRASOUND IN OBSTETRICS: FOCUS ON INTRAUTERINE GROWTH RESTRICTION. BACKGROUND, RISK FACTORS, PERINATAL OUTCOME AND POSTNATAL MOTOR AND NEURODEVELOPMENTAL OUTCOMES

Dott.ssa Scala Carolina

Tutor:

Prof. Laura Avanzino

Coordinatore:

Prof. Piero Ruggeri

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ABBREVIATIONS

FGR: fetal growth restriction
IUGR: intrauterine growth restriction
SGA: small for gestational age
AGA: appropriate for gestational age
LGA: large for gestational age
BPD: biparietal diameter
HC: head circumference
AC: abdominal circumference
FL: femur length
EWF: estimate fetal weight
ART: assisted reproductive technology
CRL: fetal crown–rump length
AMA: advanced maternal age
PE: preeclampsia
IVF in vitro fertilization
BMI: body mass index
LBW: low birth weight
ART: assisted reproductive technologies
PE: preeclampsia
IVF: in vitro fertilization
CPM: confined placental mosaicism
CVUE: chronic villitis of unknown etiology
NICU: neonatal intensive care unit
MCA: middle cerebral artery
UtA-PI: uterine artery pulsatility index
DA: diffuse adenomyosis
FA: focal adenomyosis
OE: ovarian endometrioma
DE: deep endometriosis

EXECUTIVE SUMMARY

Background

Fetal growth restriction (FGR), also known as intrauterine growth restriction (IUGR), is a common complication of pregnancy that has been associated with a variety of adverse perinatal outcomes. There is a lack of consensus regarding terminology, etiology, and diagnostic criteria for FGR and neonatal outcomes, with uncertainty surrounding the optimal management and timing of delivery for the growth-restricted fetuses. An additional challenge is the difficulty in differentiating between the fetus that is constitutionally small and fulfilling its growth potential and the small fetus that is not fulfilling its growth potential because of an underlying pathologic condition.

Objectives

The aim of this thesis was to undergo to a full review of the literature regarding terminology, etiology, diagnostic criteria and perinatal and postnatal outcomes for FGR.

In particular, the main focus of the project was to ascertain the motor and neurodevelopmental outcome of infants with FGR. During the study period we also focused our research-line on the etiology of FGR, in particular by evaluating the impact of some maternal conditions, such as adenomyosis and endometriosis, on the incidence of FGR.

CHAPTER 1. ULTRASOUND ASSESSMENT OF FETAL BIOMETRY AND GROWTH

Ultrasonography is widely used for the prenatal evaluation of growth and anatomy as well as for the management of multiple gestations. The procedure provides diagnostic findings that often facilitate the management of problems arising in later pregnancy.

Abnormal fetal growth is a leading cause of perinatal morbidity and mortality in both industrialized and developing countries. In 2005, the World Health Organization (WHO) concluded that impaired fetal growth could be related to several causes: genetic factors, maternal characteristics such as nutrition, lifestyle including smoking, age and disease; complications of pregnancy; and the physical, social and economic environment (1,2). These disorders includes fetal growth restriction (FGR), also referred to as intrauterine growth restriction (IUGR) and often associated with small-for-gestational age (SGA), and large-for-gestational age (LGA), which may lead to fetal macrosomia.

Screening for fetal growth abnormalities is an essential component of antenatal care, and fetal obstetric ultrasound plays a key role in assessment of these conditions (3).

The fetal biometric parameters most commonly used are biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur diaphysis length (FL). These biometric measurements can be used to estimate fetal weight (EFW) using various different formulae (3). It is important to differentiate between the concept of fetal size at a given timepoint and fetal growth, the latter being a dynamic process, the assessment of which requires at least two ultrasound scans separated in time. Maternal history and symptoms, amniotic fluid assessment and Doppler velocimetry can provide additional information that may be used to identify fetuses at risk of adverse pregnancy outcome. Accurate estimation of gestational age is fundamental for determining

whether fetal size is appropriate-for-gestational age (AGA). Except for pregnancies obtained from assisted reproductive technology (ART), the date of conception cannot be determined precisely. Clinically, most pregnancies are dated by the last menstrual period, though this may sometimes be uncertain or unreliable. Therefore, dating pregnancies by early ultrasound examination at 8–14 weeks, based on measurement of the fetal crown–rump length (CRL), appears to be the most reliable method to establish gestational age. Once the CRL exceeds 84 mm, HC should be used for pregnancy dating (4-6). HC, with or without FL, can be used for estimation of gestational age from the mid-trimester if a first-trimester scan is not available and the menstrual history is unreliable. When the expected delivery date has been established by an accurate early scan, subsequent scans should not be used to recalculate the gestational age (3). Serial scans can be used to determine if interval growth has been normal.

CHAPTER 1.1 *Fetal measurements: what should be measured, when and how?*

CRL should be used to assess fetal size and to estimate gestational age up to 14 weeks of gestation. After 14 weeks, usual measurements include BPD, HC, AC and FL (3,4). All measurements can be acquired transabdominally or transvaginally. Clear images with appropriate magnification and correct depiction of landmarks are needed to allow precise caliper placement (3). Calipers should be placed as described in the charts that are chosen for gestational age or size determination.

A review of measurement techniques and pitfalls can be found online on the INTERGROWTH-21st Website (7). The HC and AC measurements, can be acquired with two possible methods, which are equally reproducible: using the ellipse tool and the two-diameters method; in both cases the calipers should be placed in an outer-to-outer position (15). It is essential that, within an institution

or a referring hospital's local or national network, the same method is used, and that this is the same as that adopted in the studies which produced the reference curves being used.

CHAPTER 1.2 *Estimated fetal weight*

EFW could be used to monitor fetal size and growth (4). EFW helps clinicians to assess fetal growth, depending on which size parameters are included; use of the same anatomic parameter(s) for monitoring growth prenatally and postnatally; and communication and management with parents and pediatricians regarding the anticipated birth weight.

However, use of EFW also carries some disadvantages (10,11): in particular, errors in single-parameter measurements are frequent; accuracy of EFW is compromised by large intra- and interobserver variability, with errors in the range of 10–15% (12). Given the errors inherent in EFW, the time interval between two scans should be at least 2-3 weeks, to minimize false-positive rates for the detection of fetal growth disorders, although this recommendation does not preclude more frequently performed scans when clinically indicated (19). However, monitoring of fetal status may require interval scans with no EFW evaluation.

Quality control in fetal biometry is crucial for auditing and monitoring purposes. Image storage and review, and assessment of intra- and interobserver reproducibility are fundamental for a good quality-control strategy (5,14,15). Quality control of images for CRL, HC, AC and FL measurement can be performed using scored criteria, (Table 1) (16,17).

Table 1. Criteria for score-based objective evaluation of quality of biometric images

Type of image		
Cephalic	*Abdominal*	*Femoral*
Symmetrical plane	Symmetrical plane	Both ends of bone clearly visible
Plane showing thalami	Plane showing stomach bubble	< 45° angle to horizontal
Plane showing cavum septi pellucidi	Plane showing portal sinus	Femur occupying more than half of total image
Cerebellum not visible	Kidneys not visible	Calipers placed correctly
Head occupying more than half of total image	Abdomen occupying more than half of total image	
Calipers and dotted ellipse placed correctly	Calipers and dotted ellipse placed correctly	

CHAPTER 1.3 *Which metric should be used in describing fetal biometric and which cut-off to define abnormal biometry?*

Measurements acquired on fetal ultrasound can be recorded as raw data, expressed in mm or cm. Because measurements and their distributions change with advancing gestational age, centiles, Z-scores, percentage deviation from the mean or multiples of the median (14) may also be used when referring to raw data of a reference range. Assuming the underlying

normality of distribution of the measured parameter, centiles or Z-scores are measures of deviation from the mean of a population. The use of Z-scores has several advantages, including that the scale is linear, allowing comparison between different biometric variables at different gestational ages (18). Centiles are intuitively more understandable than are Z-scores and there is a precise

relationship between them when there is a standard normal distribution of the population (5th centile is equivalent to –1.64 Z-score; 10th centile is equivalent to –1.28 Z-score), (19).

AC and/or EFW below the 10th centile for gestation is a commonly accepted definition of FGR. However, this cut-off value changes depending on the chart used. Moreover, most SGA babies are not growth-restricted at birth, and some babies with FGR due to placental insufficiency who are at risk of compromise or stillbirth are AGA (20). An international Delphi consensus recently proposed that a cut-off of AC or EFW below the 3rd centile may be used as the only diagnostic parameter for FGR (21). In case of AC or EFW below the 10th centile, the diagnosis of FGR should be made only in association with other parameters (Table 2). Depending on the gestational age, these include maternal (uterine artery) or fetal (umbilical or cerebral/umbilical artery) Doppler findings or a drop (of more than two quartiles) in AC or EFW centile in serial scans.

Table 2 Consensus-based definitions for early and late fetal growth restriction (FGR) in absence of congenital anomalies

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3rd centile *or* UA-AEDF *Or* 1. AC/EFW < 10th centile *combined with* 2. UtA-PI > 95th centile *and/or* 3. UA-PI > 95th centile	AC/EFW < 3rd centile *Or at least two out of three of the following* 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles > 2 quartiles on growth centiles* 3. CPR < 5th centile *or* UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery. Reproduced from Gordijn *et al.*[5].

CHAPTER 1.4 *Screening for FGR and/or SGA foetuses*

A routine mid-trimester ultrasound scan is typically performed between 18 and 22 weeks of gestation (22). This period represents a compromise between dating the pregnancy (more accurate if established earlier) and the detection of major congenital anomalies. The performance of or need for any additional third-trimester scans is based on local guidelines, and the presence or absence of

maternal or fetal conditions and of risk factors that are known to be associated with abnormal growth (23).

Additional scans could be beneficial for monitoring fetal wellbeing and for subsequent detection of fetal growth abnormalities (24). Ultrasound examination at 36weeks' gestation was found to be more effective than that at 32 weeks' gestation in detecting FGR and predicting related adverse perinatal and neonatal outcome (25). Future research should include more accurate sonographic detection of FGR infants, to identify a small fetus at risk for morbidity and to determine interventions that could improve neonatal outcome (26).

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CHAPTER 2. ULTRASOUND CHARTS OF FETAL SIZE

Recent publications (1-5), editorials and correspondence, (6-9) as well as presentations and debates at national and international meetings, have activated a controversy that goes well beyond the boundaries of obstetrics and perinatal medicine. The controversies touch upon fundamental topics in biology, genetics, politics, and human rights.

At present, clinicians around the world are using many different ultrasound charts of fetal size, based on a variety of populations and methodologies, to monitor growth. All these charts are references rather than prescriptive standards. The distinction is critical.

References describe how individuals have grown at a particular time and place, often decades beforehand. Prescriptive standards, on the other hand, are purposely developed using a selected, healthy population, to describe how humans should grow when nutritional, environmental, and health constraints on growth are minimal. They are based conceptually on the WHO 1995 recommendation that "human growth should be evaluated using international standards, describing how individuals should grow", (10).

Chapter 2.1 The INTERGROWTH-21st fetal growth standards

The INTERGROWTH-21st project was a comprehensive evaluation of human growth and development across the first 1000 days of life, leading to the construction of fetal and preterm postnatal growth standards; it included an assessment of newborn body composition, infant feeding practices, and preterm postnatal growth, as well as postnatal growth and neurodevelopment evaluation at 2 years of age to assess the appropriateness of the complete cohort for the construction of standards (Panel 1).

PANEL 1
INTERGROWTH-21st project characteristics

Large prospective study of 59,137 pregnant women
Population based: all institutions providing pregnancy and delivery care in 8 geographically limited urban areas with low rates of adverse perinatal outcomes and low pollution, domestic smoke, radiation, and other toxic substances
Sampling of individual women within 8 geographic areas using predefined criteria for construction of standards
Participants followed up to age 2 y
Pregnancy, neonatal anthropometry, and perinatal conditions recorded for total population (59,137 pregnant women) in 8 geographic areas using standardized procedures, identical equipment, and centrally trained staff
Environmental conditions evaluated using special data collection form developed in collaboration with Center for Environmental Research and Children's Health, University of California, following WHO recommendations
Excluded from standards only severe maternal or fetal conditions defined a priori
A priori data analysis plan based on WHO recommendations to construct human growth standards
Use of skeletal growth measures from <14 wk' gestation to age 2 y for comparisons across populations, as recommended by WHO
Three complementary data analysis strategies to support pooling data for construction of standards

International standards for human growth from <14 wk' gestation to age 2 y
International preterm postnatal growth standards as recommended by WHO
Preterm postnatal motor development assessment following WHO milestones

Published real-time, online data management system
Ultrasound equipment selected based on predefined criteria after extensive public consultation according to WHO administrative requirements
Ultrasound measures in triplicate and corroborated by newborn anthropometry
Ultrasound results masked to operators to eliminate expected result bias
Standardized equipment at all sites for ultrasound; maternal, newborn, and child anthropometry
Ultrasound machines calibrated with standard phantom
Published system of:

- Training, standardization, and certification of ultrasound operators
- Quality-control strategy for all maternal and postnatal measures
- Assessment of intraobserver and interobserver variation of ultrasound fetal biometry
- Protocols for quality control of ultrasound image review, data monitoring, and random sample remeasurement

The first step in creating prescriptive international standards of optimal fetal growth was to select free-living populations in defined geographic areas with minimal constraints on growth, and good maternal and perinatal health outcomes. The second step was to select, from the whole population, healthy pregnant women at low risk of adverse outcomes, (11) Healthy pregnant women with a naturally conceived singleton pregnancy, who met the individual inclusion criteria (11) were identified prospectively in the INTERGROWTH-21st project.

Women were recruited <14 weeks' gestation, and pregnancies were dated based on a certain last menstrual period, but corroborated by ultrasound measurement of the CRL, (12) Ultrasound scans were then performed every 5 ± 1 weeks from the initial dating scan by dedicated research staff

using identical, midrange ultrasound machines at each study site, with rigorous training and standardization procedures (13,14) quality control measures (15), and blinding of measurements. Moreover, unlike any other longitudinal study of ultrasound in pregnancy, the infants involved in the fetal growth standards were followed up for 2 years after birth, using the same standardized methods employed in the WHO child growth standards to measure growth (16) neurodevelopment, auditory processing, and sleep-wake patterns at 2 years of age (3)

The INTERGROWTH-21st Project aimed to produce, for the first time (panel), international standards for newborn size for each gestational age based on data from its Newborn Cross-Sectional Study subpopulation, which conformed at population and individual levels to the prescriptive approach used in the WHO Multicentre Growth Reference Study (MGRS) (16)

These new standards are considered to be a conceptual and practical link to WHO Child Growth Standards, which have been adopted by more than 125 countries worldwide (17,18). The purpose is to bridge gaps in clinical and population assessments for fetuses, neonatal babies, and infants through provision of similar instruments to monitor child growth seamlessly from early pregnancy to age 5 years and to screen for stunting and wasting.

The INTERGROWTH-21st Project therefore is an international, sex-specific standards for weight, length, and head circumference for gestational age at birth that complement the available WHO Child Growth Standards and allow comparisons across populations. The international standard for length at birth for gestational age, in particular, when incorporated into routine neonatal care, will provide a method for the early diagnosis of stunting, which can be then be monitored during infancy and childhood using the corresponding WHO Child Growth Standards.

2.2 Customized growth charts

Customized charts adjust for constitutional or physiologic variation and exclude pathologic factors that affect growth, thereby defining an optimized standard that represents the growth potential of each individual fetus (19,20). As a result, they improve the prediction of birthweight in an uncomplicated pregnancy and improve the identification of abnormal growth.

In the customized model, the variables for adjustment are derived from birthweights of normally formed fetuses who were delivered at the end of uncomplicated pregnancies at term. The physiologic variables that significantly affect birthweight are consistent in many cohort studies and are quantified through multivariable analysis: fetal sex, maternal height, weight in early pregnancy, parity, and ethnic origin. Adjustment for maternal height and weight is made within normal body mass index (BMI) limits only (19). Pathologic factors that are known at the beginning of pregnancy include hypertension, diabetes mellitus, smoking, and low and high BMI. Social deprivation may appear in the univariate analysis but does not tend to remain significant after adjustment for other factors, such as smoking and abnormal BMI (21). The model adjusts for the physiologic but not pathologic variables, and results in a constant that represents an expected optimal birthweight at the end of an uncomplicated pregnancy.

The use of customized percentiles is recommended by the Royal College of Obstetricians and Gynaecologists Guidelines (22) for the assessment of birthweight and antenatal surveillance of fetal growth. Customized percentile calculators are freely available via the Gestation Network (www.gestation.net) that is administered by the Perinatal Institute and have been or are currently in use by over 300 clinicians and researchers in 30 countries. They can be applied in case-by-case assessment of neonatal weight or in spreadsheet format to analyze whole databases for audit or research.

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CHAPTER 3. FETAL GROWTH RESTRICTION (FGR)

CHAPTER 3.1 *Terminology*

FGR is defined as a rate of fetal growth that is less than normal for the growth potential of a specific infant as per the race and gender of the fetus. The terms FGR and SGA are often used interchangeably, although there are substantial differences between the two (1).

The term SGA define those fetuses whose weight is less than (less than 10th percentile for that particular gestational age) the population norms on the growth charts, however SGA refers only to birth weight without consideration to in-utero growth and placental function during pregnancy. On the contrary, FGR occurs when the fetus does not reach its intrauterine potential for growth and development as a result of compromise in placental function. A FGR infant may have an appropriate birth weight as per gestation, but may have suffered from intrauterine growth restriction as a consequence of a perinatal insult, thus FGR is a clinical definition and applied to infants with clinical evidence of malnutrition. It is important to keep in mind that neonate with a birth weight less than the 10° percentile may be SGA, but not FGR, and a neonate with a birth weight greater than the 10° percentile may be FGR (2).

CHAPTER 3.2 *Epidemiology*

It is estimated that approximately 11% of all total neonates delivered in developing countries are born every year at term with low birth weight (LBW), and this incidence is six time higher when compared to developed countries. The incidence of FGR fetuses varies among countries,

populations, races and increases with decreasing gestational age. The main incidence of these FGR infants is in Asia, which accounts for nearly three-fourth of all affected infants, followed by Africa and Latin America. For LBW and FGR-LBW respectively, the highest incidences are detected. At the national level, the highest incidences for LBW and FGR-LBW respectively are: Bangladesh (50%, 39%), India (28%, 21%) and Pakistan (25%, 18%), followed by Sri Lanka (19%, 13%); Cambodia (18%, 12%); Vietnam and the Philippines (11%, 6%); Indonesia and Malaysia (8%, 4%); Thailand (8%, 3%) and the People's Republic of China (PRC) (6%, 2%), (3).

FGR is an intercurrence in 5–10% of pregnancies (4). It is the second leading cause of perinatal mortality and is responsible for 30% of stillborn infants; it is also the most common cause of premature births and intrapartum asphyxia.

CHAPTER 3.3 *Etiology*

The etiology of FGR can be broadly categorized into maternal, fetal, and placental. Although the primary pathophysiologic mechanisms underlying these conditions are different, they often (but not always) have the same final common pathway: suboptimal placental perfusion and fetal nutrition.

- ***Chapter 3.3.1 Maternal factors***

Race and maternal age (less than 16 years and more than 35 years) have been found to be risk factors for FGR (Table 1) (5,6).

Table 1. Maternal causes for intrauterine growth restriction

- Maternal age
- Altitude
- Socioeconomic status
- Ethnicity or race
- Maternal substance abuse
- Maternal medication
- Maternal height and weight
- Parity
- Inter pregnancy interval
- Previous delivery of SGA newborn
- Assisted reproductive technologies
- Failure to obtain normal medical care in pregnancy
- Severe maternal starvation
- Hematologic medical disorders
- Maternal medical disorders
- Pathological conditions in pregnancy like preeclampsia and diabetes associated with vasculopathy
- Maternal infection and parasite infestations

Low socioeconomic status and living in a developing country is an independent risk factor for FGR. Low socioeconomic status is more often related to the mother's poor nutrition as well as substance abuse, whereas living in a developing country is associated with maternal anemia or malnutrition, which leads to FGR (7).

Advanced maternal age (AMA) is defined as childbearing in a woman over 35 years of age and is a growing trend with In high-income countries (8). This trend is most commonly attributed to older primigravid women who delay childbearing by lifestyle choice or due to underlying subfertility, but also includes multiparous women continuing childbearing (9). Women in both groups have benefited from advancements in assisted reproductive technologies (ART). AMA is reported to be associated with a wide range of pregnancy complications including: FGR, preeclampsia (PE), placental abruption, preterm birth and stillbirth (10,11) and importantly these increased risks appeared to be independent of maternal co-morbidities (12,13).

Maternal diseases that have an impact on blood circulation, may frequently cause a decrease in uteroplacental blood flow and lead to FGR. These various diseases include hypertensive disorders (gestational and non-gestational), diabetes associated with vasculopathy, chronic renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease and others. Acquired thrombophilia, such as anti-cardiolipin antibodies and lupus anticoagulant, can cause poor pregnancy outcomes, such as early-onset preeclampsia and fetal stillbirth in addition to FGR. On the contrary, inherited thrombophilia polymorphisms (namely anti-thrombin III deficiency, factor V Leiden, protein C and S deficiencies) did not result in FGR (14).

The use of ART is a risk factor for FGR both independently in singleton pregnancies and also as a result of multiple gestation pregnancies . Singleton pregnancies obtained with ART has been shown to be related with adverse obstetrical and perinatal outcomes, but this is challenging literature to analyse. In almost all studies of singleton pregnancies resulting from any type of ART, LBW is found more often than in spontaneous pregnancies (15). Many emerging studies are trying to identify the causative factors responsible for growth disturbance in women undergoing ART by comparing outcomes in various subsets within cohort studies of the AHR population and with outcomes in spontaneous pregnancies. Sasanova et al. performed logistic regression analysis on 8941 singleton pregnancies after in vitro fertilization (IVF) to determine predictive factors for preterm birth and LBW. They found that primiparity, smoking, BMI, and the vanishing twin phenomenon increased the risk of preterm birth, and that maternal age, smoking, and duration of infertility increased the risk of LBW (16).

Women in the lowest quartile of both low pre- pregnancy weight, and pregnancy weight gain are at the highest risk of producing an FGR infant (17). A short and longer inter-pregnancy interval has been found to be associated with FGR. Zhu et al. showed that when compared to infants conceived 18–23 months after a live birth, infants conceived less than six months after a live birth had higher

odds for low birth weight, preterm birth and SGA; and similarly the infants conceived 120 months or more after a live birth had higher chances of adverse outcomes even when controlled for other confounding variables (18).

Cigarette smoking is a common cause of FGR (19-21). There are a number possible of mechanisms, including nicotine-induced placental vasoconstriction (22) and the effects of carbon monoxide on mitochondrial function (23). Research on rats has shown that nicotine damages the fetal pancreatic mitochondria leading to beta cell dysfunction and apoptosis. This causes impaired glucose tolerance in the off-spring, which may be irreversible if nicotine exposure continues during lactation (24). Inadequate insulin production in the fetus would impair glucose uptake , which could be a contributory mechanism for the impaired fetal growth. An adverse effect of maternal smoking may persist into childhood; children exposed to cigarette smoke in utero tend to have a higher body mass index (BMI), which is not totally attributable to their lower birthweight (25), and there are also gender differences in the childhood growth patterns, with greater weight gain in boys (26). Cigarette smoking also predisposes to gestational diabetes (27).

Passive smoking has also been associated with FGR. A cross-sectional study performed by Goel et al. assessed the effects of passive smoking during pregnancy and found out that women who have been exposed to passive smoking had significantly higher incidence of preterm birth and SGA babies as compared to unexposed mothers (28). Similar results were shown by study from Malaysia that reported a significant association between second hand smoke exposure during pregnancy and LBW (29).

Heavy maternal drinking is associated with fetal alcohol syndrome, whereas moderate alcohol consumption has been associated with FGR (30,31). Toxic exposures of mother, including various medications, such as warfarin, steroids, anticonvulsants, antineoplastic agents, anti-metabolite and

folic acid antagonists result in FGR (32). Maternal intake of illicit drugs like marijuana or cocaine during pregnancy is associated with impaired fetal growth (33).

Maternal infection and parasite infestations, such as TORCH, malaria, tuberculosis, urinary tract infections and bacterial vaginosis has been implicated in FGR (34).

Several studies have reported in the last decade a correlation between endometriosis and major adverse obstetric outcomes, such as spontaneous late miscarriage, preterm prelabor rupture of the membranes and preterm birth, SGA, hypertension, preeclampsia, gestational diabetes, obstetric hemorrhage and placenta previa (35-37). Theoretically, some pathogenic mechanisms might explain the higher risk of obstetric complications in women with endometriosis; these mechanisms include endometrial resistance to selective actions of progesterone, inflammation, inadequate uterine contractility, endometrial excessive activation of free radical metabolism and abnormal trophoblastic invasion into the 'myometrial junctional zone' due to partial or absent remodeling of the myometrial spiral arteries (38). However, other studies and a systematic review did not confirm completely these findings (39).

- ***Chapter 3.3.2 Placental factors***

The placenta is a complex organ with a biologically short existence and it is the only organ formed by cells from two different organisms. The placenta is an essential organ for the transfer of nutrients and gases from the mother to fetus and for the elimination of products resulting from fetal metabolism. Blood flows to the uterus through the uterine arteries, irrigating and providing nutrients to the intervillous space, which is composed of 100–200 uteroplacental arteries. It also includes about 75–175 veins, which provide oxygenated blood to the fetus (40).

The placenta has also the function of a barrier, protecting the fetus from different pathogens. Moreover, It has the ability to act as an endocrine organ, because it is able to synthetize and realize hormones, growth factors, and cytokines (41).

The interaction between maternal and fetal circulations within the placenta is fundamental for adequate exchange of nutrients and oxygen. It is hypothesized that this adaptation comes from a physiological process referred to as “waves of trophoblast migration”. Cytotrophoblast invasion, during the first trimester of pregnancy, happens in the decidual tissue, including the intradecidual segments of the spiral arteries. The second migration occurs between the 16th and 18th weeks, when endovascular invasion extends to the myometrial segments of the spiral arteries that lose the musculoskeletal layer, which is replaced by the fibrin matrix. This process leads to a drop in vascular resistance, in addition to less responsiveness to local vasoconstricting agents (42, 43).

Abnormal placentation has been defined as a condition in which trophoblast invasion of the myometrial portion of the spiral arteries does not occur (44). Reduced uteroplacental perfusion associated with maternal vascular disease is responsible for 25–30% of FGR cases; it is the most common cause in non-anomalous fetuses.

Placental weight has fundamental role in FGR determination. In 2001 Heinonen et al. evaluated the association between placental weight and birth weight in AGA and SGA infants. What they found was that placenta of SGA infants was 24% smaller in size than that of AGA infants. Placental actual weight was also lower in SGA infants than in AGA infants of the same birth weight (45).

Structural abnormalities and changes in placental implantation and attachment may also be involved in the etiology of FGR, including bilobed placenta, low-insertion placenta, chorioangioma, velamentous insertion of the umbilical cord, and presence of a single umbilical artery. These anomalies may lead to a decreased transfer of nutrient and oxygen to the fetus, leading to FGR (46, 47).

Confined placental mosaicism (CPM) are chromosomal anomalies (usually involving a trisomy) found in the placenta, but not in the fetus. Wilkins-Haug et al. in their study evaluated 70 FGR infants and 70 AGA infants and reported that CPM occurred significantly more in FGR infants placentae compared to AGA infants with high-level tetraploidy among the FGR placentae. These placentae histologically had greater decidual vasculopathy, infarction and intervillous thrombus formation predominantly in the karyotypically abnormal placentae (48).

Chronic villitis of unknown etiology (CVUE), is characterized by focal areas of inflammation with mononuclear cells and areas of fibrinoid necrosis in chorionic villi, and is a diagnosis of exclusion. CVUE is detected in 7– 33% of placentas, mainly with FGR, unexplained prematurity, preeclampsia, perinatal asphyxia and intrauterine fetal death (49).

- ***Chapter 3.3.3 Fetal factors***

Fetal chromosomal abnormalities account for 7–19% of total FGR infants born (Table 2). The most common chromosomal anomalies are trisomies, in particular trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome).

Table 2. Fetal factors for intrauterine growth restriction

• Chromosomal abnormalities • Genetic syndromes • Major congenital anomalies • Multiple gestation • Congenital infections • Metabolic disorders

A study published in 1993, reported incidence of chromosomal abnormalities of 19% in FGR foetuses, with most common chromosomal defect in the group referred before 26 weeks of gestation being triploidy and thereafter most common being trisomy 18 (50). Another study, published by Anandakumar et al. reported incidence of chromosomal defects of 9.9% in the FGR fetuses (51). The pathogenesis that has been purposed is the reduction of number of small muscular arteries in the tertiary stem villi of the placenta and also increased vascular resistance of the placenta (52).

Many congenital anomalies have been found to be associated with FGR. The most common ones includes tracheo-esophageal fistula, congenital heart disease (53), congenital diaphragmatic hernia (54), abdominal wall defects, such as omphalocele and gastroschisis, neural tube defect like anencephaly and anorectal malformation. Congenital malformations, account for approximately 1–2% of FGR. Khoury et al. performed a population-based study and found out that the incidence of FGR among malformed infants was 22,3% (relative risk 2,6) and also reported that the frequency of FGR increased with increasing number of defects in the infant from 20 to 60% (55).

Congenital infection are responsible for about 5% of the total FGR cases. In developed countries, the most common infections are toxoplasmosis and cytomegalovirus, while it has been observed a reduction of rubella because of vaccination and the strategy for routine screening for TORCH (56). In the developing countries the common causes are malaria, congenital HIV infection, syphilis and rubella. In Africa and South-East Asia, malaria is the predominant infectious disease and account for 40% of cases in places where it is endemic (57, 58). Malaria activates immune-mediated inflammatory processes and platelets, which deposit in the vascular system and lead to vessel obstruction and decrease nutrition supply to fetus leading to FGR (59).

Multiple gestations are reported to be associated with about 3% of cases of FGR. This is more common in monochorionic twins or higher order gestation. The growth velocity in twin pregnancies

is usually normal till 28 weeks of gestation and then there is a physiological decrease in the growth rate. A growth discordant of 15% or greater occurs in around 30% of twin pregnancies, and it has been attributed to ‘‘uterine overcrowding’’ (60, 61).

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CHAPTER 4 STUDY 1*:*

Influence of adenomyosis on pregnancy and perinatal outcomes in women with endometriosis

INTRODUCTION

Endometriosis and adenomyosis are defined by the presence of endometrial glands and stroma, located outside the uterus and in the myometrial wall, respectively (1). The eutopic endometrium and the inner myometrium in patients affected by endometriosis and/or adenomyosis show several functional and structural abnormalities (1). These differences seem to be related mainly to abnormal expression of genes involved in local estrogen production and response to progesterone, an altered oxidative stress response, and the presence of cytokines, inflammatory mediators and apoptotic markers (2,3). In the past 10 years, several studies have reported a correlation between endometriosis and major adverse obstetric outcomes, such as spontaneous late miscarriage (4), preterm prelabor rupture of the membranes and preterm birth (5–11), small-for-gestational age (SGA), (5,10), hypertension (9), pre-eclampsia (5,8,11), gestational diabetes (10), obstetric hemorrhage (such as abruptio placentae and postpartum bleeding) (5,9,11) and placenta previa (5–7,9,12).

However, other studies (12,13) and a systematic review (14) did not confirm completely the increased risk of obstetric complications in women with endometriosis. Theoretically, some pathogenic mechanisms might explain the higher risk of obstetric complications in women with endometriosis; these mechanisms include endometrial resistance to selective actions of progesterone, inflammation, inadequate uterine contractility, endometrial excessive activation of free radical metabolism and abnormal trophoblastic invasion into the 'myometrial junctional zone'

due to partial or absent remodeling of the myometrial spiral arteries (15). It is well known that there is a strong association between endometriosis and adenomyosis16. The reported prevalence of adenomyosis in patients affected by endometriosis ranges widely between 20% and 50% (17–19) and its association seems to be related to increasing age, parity, dysmenorrhea intensity and presence of deep infiltrating endometriosis (DIE), (20). Previous studies also showed that women with adenomyosis are at increased risk of some adverse pregnancy outcomes, such as preterm delivery, preterm prelabor rupture of membrane, SGA and fetal malpresentation (21–23). However, despite this background, previous studies have given little attention to the influence of adenomyosis on the pregnancy outcome of patients with endometriosis. On the basis of these premises, the aim of the present study was to evaluate maternal and fetal outcomes in a cohort of women with endometriosis with or without the concomitant presence of diffuse or focal adenomyosis.

METHODS

Study design and study population

This study was based on a retrospective analysis of data collected prospectively between January 2014 and December 2016. The study protocol was approved by the regional ethics committee. Patients included in the study signed a general consent form for the use of their data for scientific purposes. This study included pregnant women who had ultrasonographic and/or histological diagnosis of endometriosis with or without ultrasonographic diagnosis of focal or diffuse adenomyosis prior to conception. The ultrasonographic exams were performed at any phase of the menstrual cycle, regardless of the use of hormonal therapy. Standardized ultrasound criteria were used for the diagnoses of DIE (24) and endometriomas (25). The ultrasonographic diagnosis of adenomyosis was made if two or more of the following features were present: asymmetrical myometrial thickening, myometrial cysts, linear striations, hyperechoic islands or an irregular and

thickened endometrial–myometrial junctional zone on either two- or three-dimensional imaging (26,27). On ultrasonography, focal adenomyosis was defined as the presence of adenomyosis-related lesions in only one part of the myometrium, while diffuse adenomyosis was defined as the presence of ill-defined lesions in more than one site within the uterine wall, more often being dispersed within the myometrium rather than forming a confined lesion (28).

The patients included in the study were divided into three groups: those with endometriosis and focal adenomyosis, those with endometriosis and diffuse adenomyosis and those with endometriosis only. Women with previous uterine surgery or uterine malformation, pregnancies with major fetal structural abnormality, chronic hypertension, known autoimmune disease or fetal aneuploidy, and multiple gestations were excluded.

Pregnancies were dated by measurement of crown–rump length in the first trimester according to the National Institute for Health and Care Excellence (NICE) guidelines (29). Pregnancy-associated plasma protein-A (PAPP-A) levels were measured at the time of routine 11–14-week first-trimester combined screening test for Down syndrome. Uterine artery (UtA) Doppler indices were measured in all women at the 11–14-week examination and at the time of the routine anomaly scan between 19 and 23weeks of gestation. UtA Doppler assessment was performed transabdominally (30). The pulsatility index (PI) of the left and right UtAs was averaged to compute a mean PI and plotted against a published reference range (30). All patients underwent a growth scan during the third trimester of pregnancy between 29 and 34weeks of gestation to evaluate growth of the fetus. Low-dose aspirin for prevention of pre-eclampsia was not used during the study period. Ultrasound assessments were performed using a GE Voluson E6 ultrasound machine (GE Medical Systems, Zipf, Austria). Maternal characteristics, including age, body mass index (BMI), ethnic origin and mode of conception (spontaneous or in-vitro fertilization), were recorded during the first visit and pregnancy

outcomes were collected. Delivery or follow-up scans were arranged as appropriate for any suboptimal assessments.

Gestational complications were defined as follows: preterm birth as delivery before 37 completed weeks of gestation; pregnancy-induced hypertension as blood pressure persistently over 140/90mmHg that developed after 20weeks of gestation in a previously normotensive woman; pre-eclampsia as gestational hypertension and proteinuria (>300 mg/24 h); and SGA as birth weight<10th centile for gestational age.

Statistical analysis

Data distribution was assessed according to the Kolmogorov–Smirnov test of normality. Data were expressed as mean±SD, or median and interquartile range. Categorical variables were described as number (%). The correlation between continuous variables was assessed using Pearson's coefficient or Spearman's rho. Pearson's chi-square test was used to analyze categorical variables. Student's independent t-test and the Mann–Whitney U-test were used to compare continuous variables, as appropriate. Mean UtA-PI Z-score and birth-weight centile were calculated from the appropriate reference ranges (30). Mean UtA-PI was corrected for gestational age and multiples of the median were calculated based on reference ranges from the published centiles (30). Logistic regression analysis was used to assess the associations of maternal characteristics, first- and second-trimester markers, and fetal outcome with SGA in women with endometriosis and diffuse adenomyosis and those with endometriosis and focal adenomyosis. $P<0.05$ was considered statistically significant. Statistical analysis was performed using the statistical software package SPSS Statistics version 20.0 (IBM Corp.,Armonk, NY, USA).

RESULTS

Demographic and pregnancy characteristics of the three groups of patients are presented in Tables 1 and 2. During the study period, 206 pregnant women with endometriosis were recruited into the study and completed the required follow-up. Among these patients, 148 (71.8%) had endometriosis only, 38 (18.4%) had focal adenomyosis and 20 (9.7%) had diffuse adenomyosis. Compared with women with endometriosis only, those presenting with diffuse adenomyosis had significantly lower BMI and first-trimester PAPP-A level, and significantly higher first-trimester and mid-pregnancy mean UtA-PIs. The prevalence of a SGA fetus, calculated according to ultrasound-estimated fetal weight centile at the third-trimester ultrasound assessment, was significantly different between women with endometriosis only (10.8%) and those with diffuse adenomyosis (30%, $P<0.05$). These results were confirmed after delivery, with the prevalence of SGA birth in women presenting with endometriosis only and that in women with diffuse adenomyosis being 10.8% (n=16) and 40% (n=8), respectively ($P<0.05$). No statistically significant difference was found in 5-min Apgar score or in the prevalence of pre-eclampsia between the two groups of patients (Table 1).

Compared with women with endometriosis only, those presenting with focal adenomyosis did not have significantly different maternal demographics, first-trimester PAPP-A level, first-trimester and mid-pregnancy mean UtA-PIs, estimated fetal weight centile or prevalence of SGA fetus. Moreover, no statistically significant difference was found in prevalence of SGA at birth, 5-min Apgar score or prevalence of pre-eclampsia between the two groups (Table 1). Logistic regression analysis was used to assess the relationships of maternal and pregnancy characteristics with SGA at birth in those with diffuse adenomyosis and those with focal adenomyosis (Table 2). The presence of diffuse adenomyosis was the only parameter associated independently with the delivery of a SGA infant.

Table 1. Demographic and ultrasound variables and outcome in pregnant women with endometriosis, subdivided into those with associated diffuse adenomyosis (DA), those with associated focal adenomyosis (FA) and those with endometriosis only

	Focal adenomyosis and endometriosis (n=38)	**P value**	**Diffuse adenomyosis and endometriosis** (n = 20)	**P value**	**Endometriosis only** (n = 148)
Demographics					
Maternal age, (years, median, IQR)	30 (26.5-33)	0.849	31.0 (27.0-33.0)	0.522	30.0 (27.0-33.0)
Nulliparous (n, %)	36 (94.7)	0.069	18 (90.0)	0.431	123 (83.1)
BMI (kg/m^2, median, IQR)	25.2 (22.4-28.5)	0.265	21.2 (19.5-24.2)	0.043	23.7 (20.9-26.5)
Race (n, %) • Caucasian • Afro-Caribbean • Asian	31 (81.6) 5 (13.2) 2 (5.3)	0.907	17 (85.0) 2 (10) 1 (5.0)	0.993	125 (84.5) 16 (10.8) 7 (4.7)
ART (n, %) • FIVET/ICSI • IUI	6 (15.8) 6 (15.8) 0 (0)	0.634	4 (20.0) 4 (20.0) 0 (0)	0.382	19 (12.8) 17 (11.4) 2 (1.4)
Previous early miscarriage (n, %)	4 (10.5)	0.252	1 (5.0)	0.940	8 (5.4)
Smoking (n, %)	5 (13.2)	0.790	3 (15.0)	0.987	22 (14.9)
Surgical/histological diagnosis of endometriosis (n, %)	/	/	/	/	47 (31.8)
USG diagnosis of endometriosis (n,%)	17 (20)	/	17 (20)	/	132 (89.2)
Ovarian endometrioma, (n, %)	21 (55.3)	0.835	11 (55)	0.891	79 (53.4)
Rectovaginal endometriosis, (n,%)	15 (39.5)	0.787	9 (45)	0.792	62 (41.9)
Colorectal endometriosis, (n, %)	8 (21.0)	0.672	5 (25)	0.947	36 (24.3)
Uterosacral endometriotic nodule, (n, %)	6 (15.8)	0.634	3 (15)	0.788	19 (12.8)

Bladder endometriosis, (n, %)	0 (0)	0.471	0 (0)	0.601	2 (1.3)
1st and 2nd trimester variables					
PAPP-A (MoM, median, IQR)	0.84 (0.66-1.2)	0.286	0.61 (0.41-0.83)	<0.05	0.88 (0.62-1.54)
BhCG (MoM, median, IQR)	0.88 (0.56-1.31)	0.725	1.11 (0.89-1.45)	0.117	0.90 (0.58-1.44)
Mean UtA PI 1st trimester (median, IQR)	1.61 (±0.45)	0.526	2.23 (±0.63)	<0.05	1.67 (±0.53)
Mean UtA PI 2nd trimester (median, IQR)	0.92 (±0.22)	0.669	1.30 (±0.47)	<0.05	0.94 (±0.28)
Scan assessment during the 3rd trimester of pregnancy					
Gestational age 3rd trimester scan	31.6 (33.2-30.5)	0.815	31.5 (30.3-33.3)	0.889	31.6 (30.5-33.2)
EFW (g, mean, SD)	1850 (±268)	0.671	1661 (±265)	<0.05	1873 (±301)
EFW centile (mean, SD)	49.6 (34.6)	0.755	29.0 (±20.9)	<0.05	51.5 (±32.0)
SGA fetuses (n,%)	8 (21.1)	0.093	6 (30)	<0.05	16 (10.8)
Pregnancy and perinatal outcome					
Gestational age delivery (median, IQR)	39.4 (37.7-40.5)	0.573	39.2 (38.2-39.8)	0.787	
Birth Weight (mean, SD)	3250 (±643)	0.517	2883 (±397)	<0.05	3315 (±523)
Birth weight (centile, mean, SD)	46.7 (±30.5)	0.613	22.1 (±19.3)	<0.05	49.4 (±28.7)
SGA (n, %)	8 (21.1)	0.093	8 (40)	<0.05	16 (10.8)
5 minute Apgar <7 (n, %)	2 (5.3)	0.743	2 (10)	0.241	6 (4.1)
Preeclampsia (n, %)	6 (15.8)	0.153	4 (20)	0.089	12 (8.1)

Data are shown as median (interquartile range), mean (standard deviation) or number (%).

Assisted Reproductive Technologies: ART; Endometriosis and Focal Adenomyosis: EFA; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

Table 2. logistic regression analysis for prediction of small for gestational age at birth in women with endometriosis

Variable	OR	95% CI	p-value
BMI	1.004	0.919-1.097	0.932
PAPP-A (MoM)	0.943	0.424-2.097	0.886
Uterine Artery mean PI (2nd	2.926	0.848-10.093	0.089
Diffuse adenomyosis	3.744	1.158-12.099	0.027
Focal adenomyosis	2.274	0.878-5.892	0.091

Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI; Odds Ratio: OR; MoM: multiples of the median

DISCUSSION

Main findings

The study demonstrates that the presence of diffuse adenomyosis in pregnant women with endometriosis is associated with an increased risk of delivery of a SGA infant. When assessed in isolation, conventional risk factors for placental insufficiency, such as BMI, PAPP-A and mean UtA-PI during the first and second trimesters of pregnancy, showed a strong correlation with the presence of diffuse adenomyosis in patients with endometriosis. At the time of the third-trimester ultrasound assessment, the prevalence of a SGA fetus was significantly higher in the cohort of patients with diffuse adenomyosis compared with those with endometriosis only, and these data were confirmed after delivery. After adjusting the results for potential confounding variables, such as BMI and PAPP-A, logistic regression analysis demonstrated that only the presence of diffuse adenomyosis was associated with SGA at birth, while that of focal adenomyosis was not associated with delivery of a SGA infant.

The study results strongly suggest that, in women with endometriosis, diffuse adenomyosis increases the risk of having a SGA infant and they support a potential causative relationship between diffuse adenomyosis and impaired placentation and subsequent development of SGA.

Interpretation

In the past 10 years, research has been focused on the influence of endometriosis on pregnancy outcome (4–13, 31–34). The data reported in the current literature are controversial and a systematic review concluded that there is no evidence that endometriosis has a major detrimental effect on pregnancy outcome (14). However, the review found a correlation between endometriosis and placenta previa, with odds ratios ranging from 1.67 to 15.114. In a recent retrospective case–control study including women with a singleton pregnancy conceived by in-vitro fertilization, Benaglia et al. found that women with endometriosis do not have an increased risk of preterm birth, hypertensive disorders, gestational diabetes, SGA or large-for-gestational-age newborns and neonatal problems (12). In contrast, the authors confirmed that placenta previa was more common in women with endometriosis than in controls. Surprisingly, most published studies have not assessed the impact of adenomyosis on pregnancy outcome of patients with endometriosis.

This is due to the fact that, in most of the studies, data were collected and analyzed retrospectively (7,12,13,31,33), based on computerized nationa (l4–6,8,11) or institutional (32) databases, or collected only at the time of delivery (10,34); therefore, preconceptional ultrasonographic assessment of adenomyosis was not performed. Very recently, a cohort study found no significant difference in the incidence of complications during the pregnancy and delivery of patients with rectovaginal DIE in those with and those without an ultrasound diagnosis of adenomyosis9. However, in this study, the small sample size may have limited the strength of the analysis; in fact, only 30 patients with posterior DIE and adenomyosis were compared with 22 patients with posterior

DIE without adenomyosis; furthermore, no subanalysis according to type of adenomyosis was performed (9). Our study investigated, for the first time in the literature, the influence of diffuse and focal adenomyosis on adverse pregnancy outcome in a cohort of patients with endometriosis, revealing that the concomitant presence of diffuse adenomyosis in pregnant women with endometriosis is an important risk factor for placental insufficiency and consequent delivery of a SGA infant. Adenomyosis seems to affect the process of junctional zone spiral artery remodeling from the onset of decidualization, and results in vascular resistance and increased risk of defective deep placentation (35). Yorifuji et al. measured blood flow in the myometrium and placenta using time-slip magnetic resonance angiography in women with adenomyosis who had severe fetal growth restriction, and they found that the uterine adenomyosis area showed abundant blood flow while the placenta had diminished blood flow, suggesting that unbalanced perfusion of the placenta may be among the possible causes of SGA (36). Furthermore, a case–control study in a cohort of 2138 pregnant women found that those with adenomyosis have a higher rate of preterm delivery and preterm prelabor rupture ofmembranes, probably due to increased local inflammatory response and higher levels of prostaglandins found in these patients (22). More recently, a Japanese retrospective study based on the review of a computerized database compared the pregnancy outcome of 36 women diagnosed with adenomyosis before conception with that of 144 control women without uterine abnormality (23).

The authors found that women with adenomyosis have higher risks of preterm delivery, preterm prelabor rupture of membranes, SGA infant, fetal malpresentation and Cesarean delivery (23). In agreement with these findings, another Japanese retrospective case–control study, including 49 singleton pregnancies complicated by adenomyosis and 245 controls, showed that patients with adenomyosis have increased risks of second-trimester miscarriage, pre-eclampsia, placental malposition and preterm delivery (21).

Strengths and limitations

This study has some limitations. First, it is a retrospective study, although the data were collected prospectively. Second, the sample size was relatively small, especially in the subgroup analysis. The small number of pregnant women with endometriosis and adenomyosis did not allow further subanalysis to be performed according to the type of endometriosis diagnosed by ultrasonography (i.e. ovarian endometriomas or DIE). However, these preliminary findings may pave the way for future studies with a larger sample size. Finally, we did not exclude patients who conceived by assisted reproductive technology, and this could be a potential bias on the prevalence of adverse pregnancy outcome, such as pre-eclampsia, even though the number of these conceptions was quite small and similar between the study groups. The main strength of this study is that the subgroups of women with diffuse adenomyosis and those with focal adenomyosis were considered separately when compared with those with endometriosis only, allowing a clear understanding of the role of the different forms of adenomyosis in the development of adverse pregnancy outcome.

Conclusions

In conclusion, the current study shows that diffuse adenomyosis in pregnant women with endometriosis is strongly associated with delivery of a SGA infant. Women with endometriosis and diffuse adenomyosis should be treated as being at high risk of placental dysfunction and might need closer monitoring during pregnancy. These results are also potentially useful for preconception and prenatal counseling of women with both adenomyosis and endometriosis.

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CHAPTER 5 STUDY 2:

Impact of Endometriomas and Deep Infiltrating Endometriosis on Pregnancy Outcomes and on First and Second Trimester Markers of Impaired Placentation

INTRODUCTION

Endometriosis is a chronic estrogen-dependent gynecologic disorder affecting at least 3.6% of women of reproductive age (1). Pro-inflammatory alterations of both peritoneal cavity and eutopic endometrium have been demonstrated in patients with this hormone-dependent chronic disease, who often suffer from pain symptoms and infertility (2). Eutopic endometrium and inner myometrium of these women have been demonstrated to have structural and functional abnormalities, not only due to the abnormal expression of genes that are critical for locally producing estrogens and responding to progesterone, but also to alteration of oxidative stress response, presence of inflammatory mediators, cytokines, and various apoptotic markers (3–5).Due to these abnormalities, endometriosis has been associated with defective deep placentation and several obstetrics adverse outcomes (6). In the literature, several studies reported a correlation between his benign chronic disease and higher risk of spontaneous late abortion (7), preterm premature rupture of the membranes and preterm birth (8–14), small for gestational age (SGA) (8–14), pregnancy-induced hypertension (12) and pre-eclampsia (8,11), gestational diabetes (13), and placenta previa (8–10,12,14),and other obstetric hemorrhages (such as abruptio placentae and postpartum bleeding) (11,13,14) have been reported for these patients. However, some other

studies (15,16) did not definitively confirm the higher risk some of these major obstetric adverse outcomes; thus, this topic remains controversial (17).

Our academic group recently demonstrated that the presence of di use adenomyosis in women with endometriosis was more strongly associated with impaired placentation and delivery of SGA infants in comparison to patients with only endometriosis and with focal adenomyosis and concomitant endometriosis (18); notably, these data may suggest a potential major role of adenomyosis in enhancing the risk of having these obstetrics adverse outcomes.

However, despite this background, the role of each endometriotic phenotypes, in particular ovarian endometrioma (OE) and deep endometriosis (DE), as specific risk factor for developing adverse perinatal outcomes in women with endometriosis, has been not yet investigated. This study aimed to investigate if perinatal and maternal outcomes, particularly with regard to prevalence of SGA infants, are different in pregnant women with OE versus those with DE without OE.

MATERIALS AND METHODS

Study Design and Population

This study was done by performing a retrospective analysis of a prospective database collected between January 2017 and June 2018. Women included in the study signed a general consent form for using their clinical data for scientific purposes. The research on humans has been performed by respecting of all the relevant national regulations and institutional policies, in accord to the tenets of the Helsinki Declaration. This study was approved by the Regional Ethic Committee (372REG2017; approval 12 Jan 2018).

Pregnant women with ultrasonographic diagnosis of endometriosis prior to conception were included. The ultrasonographic assessment was performed at any phase of the menstrual cycle regardless of the administration of hormonal treatment (estroprogestins and progestins).

Standardized ultrasonographic criteria were employed for the diagnosis of DE (19) and OE (20); in particular, women with rectosigmoid endometriosis underwent a detailed assessment of intestinal symptoms and a rectal water contrast transvaginal ultrasonography in order to estimate the risk of sub occlusion prior to trying to spontaneously conceive (21,22).

The patients were divided into three groups: women with OE, women with DE without OE, and women without endometriosis (controls). The controls were matched on the basis of age and parity. The controls were selected as the first patient who delivered at our institution, had no prior diagnosis of endometriosis and no symptoms suggestive of this disease (defined as presence of dysmenorrhea, deep dyspareunia, and/or chronic pelvic pain that require analgesic therapy), and had the same range of age of the cases with endometriosis (defined as 18–25, 26–30, 31–35, 35–40, and >41 years old).

Women with previous ultrasonographic diagnosis of uterine adenomyosis (23), with chronic hypertension disease, previous uterine surgery or malformations, and known autoimmune diseases were excluded. Previous surgery for endometriosis was not considered an exclusion criterion for the study if, after surgery, the presence of persistent or recurrent endometriosis was demonstrated at the ultrasonographic assessment. Moreover, pregnancies characterized by major fetal structural abnormalities and/or fetal aneuploidy, obtained by assisted reproductive techniques (ART) and multiple gestations were excluded.

In the first pregnancy-trimester, the measure of crown–rump length (CRL) was used for dating pregnancies according to the NICE (National Institute for Health and Clinical Excellence) guidelines (24).

At the time of 11–14 weeks of pregnancy, PAPP-A levels were measured as first-trimester combined screening test for Down syndrome. Both at the time of routine ultrasonography at 11–14 weeks and

of routine anomaly abdominal ultrasonography at 19–23 weeks of pregnancy, uterine artery (UtA) Doppler indices were evaluated; pulsatility index (PI) of the left and the right UtA was averaged to obtain mean PI, which was plotted against a published reference range (25). During the routine anomaly scan, cervical length was measured by transvaginal ultrasonography following standard parameters: a short cervix was defined if characterized by length 25 mm (26); the suggestion of daily use of vaginal progesterone (200 mg, micronized progesterone capsules) and bed rest were given to women with short cervix in order to prevent preterm birth, according to our institution protocol. During the third pregnancy trimester, at 29–34 weeks, an ultrasonographic scan was done in all the patients to evaluate fetus growth. The administration of aspirin at low-doses as prevention for preeclampsia was not allowed during the study period.

GE Voluson E6 (GE Healthcare, Zipf, Austria) was employed for all the ultrasonographic assessments. At the first study visit, baseline maternal characteristics, including age, ethnic origin, and body mass index (BMI) were recorded. The maternal and neonatal outcomes of each pregnancy were collected. Delivery or follow-up scans were arranged as appropriate for any suboptimal assessments.

Gestational complications were defined with standardized criteria: pregnancy induced hypertension (PIH), detecting after 20 gestation weeks a blood pressure persistently over 140/90 mmHg in a woman with previously normal pressure values; preeclampsia, in case of gestational hypertension and concomitant proteinuria (>300 mg/24 h); preterm birth, indicating a delivery before the completion of 37 gestation weeks; and SGA, in case of an infant with birth weight less than the 10th centile for gestational age.

Statistical Analysis

The Kolmogorov–Smirnov test of normality was used for assessing the distribution of data, which were expressed as mean (SD), or median and interquartile range as appropriate. Categorical

variables were described as number (%). The correlations between continuous variables were evaluated by Pearson coefficient or by Spearman rho and those between categorical variables were evaluated by Pearson x2 test. Continuous variables were compared by Mann–Whitney and independent t-tests.

Mean UtA Doppler PI, estimated fetal weight (EFW) centiles, and z-scores were calculated by using appropriate previously described reference ranges (24). Mean UtA Doppler PI was corrected for gestational age; multiple of medians were calculated by using the reference ranges extracted from the published centiles (24). Logistic regression analysis was used to evaluate the association between maternal characteristics, first- and second-trimester markers, and fetal outcomes for women with OE and DE without OE; $P < 0.05$ was considered statistically significant. Appropriate statistical software (SPSS 20.0; SPSS Inc, Chicago, IL) was employed for the statistical data analysis.

RESULTS

Table 1 reports the demographic and pregnancy-related characteristics of women of the study.

Table 1. Comparison between pregnant women with ovarian endometriomas and deep endometriosis and women without endometriosis

	DE (n = 40)	**OE** (n = 40)	**No Endo** (n = 80)	**P value (OE vs no Endo)**	**P value (DE vs no Endo)**
Demographics					
Maternal age, (years, median, IQR)	30.2 (26.8-33)	30.4 (27.75-33)	30.3 (27.0-33.0)	0.933	0.882
Nulliparous (n, %)	34 (85.0)	35 (87.5)	69 (86.2)	0.849	0.853
BMI (kg/m^2, median, IQR)	24.8 (20.4-27.2)	23.8 (21.0-25.3)	25.1 (21.5-26.7)	0.152	0.763
Race (n, %)					
• Caucasian	31 (77.5)	32 (80.0)	73 (91.2)		
• Afro-Caribbean	6 (15.0)	4 (10.0)	5 (6.2)		
• Asian	3 (7.5)	4 (10.0)	2 (2.5)	0.143	0.110
• Others	0 (0)	0 (0)	0 (0)		
Previous early miscarriage (n, %)	2 (5.0)	2 (5.0)	4 (5.0)	1.000	1.000
Smoking (n, %)	5 (12.5)	5 (12.5)	18 (22.5)	0.190	0.190
Surgical/histological diagnosis of disease (n, %)	12 (30.0)	11 (27.5)	-	-	
• Rectovaginal, (n, %)	18 (45.0)	-	-	-	
• Colorectal, (n, %)	5 (12.5)	-	-	-	
• Uterosacral, (n, %)	23 (57.5)	-	-	-	
• Bladder, (n, %)	1 (2.5)	-	-	-	
1st and 2nd trimester variables					
PAPP-A (MoM, median, IQR)	1.17 (0.64-1.56)	0.99 (0.58-1.37)	1.09 (0.66-1.55)	0.411	0.502
BhCG (MoM, median, IQR)	1.18 (0.66-1.42)	1.13 (0.56-1.59)	1.01(0.56-1.36)	0.384	0.205
Mean UtA PI 1st trimester (median, IQR)	1.67 (1.37-1.90)	1.96 (1.33-2.03)	1.64 (1.28-1.98)	0.590	0.806
Mean UtA PI 1st trimester z-scores (mean, SD)	- 0.09 ± 1.37	0.03±1.59	-0.15 ±1.58	0.553	0.850
Mean UtA PI 2nd trimester (median, IQR)	0.94 (0.74-1.12)	0.92 (0.76-1.06)	0.96 (0.75-1.13)	0.591	0.733
Mean UtA PI 2st trimester z-scores (mean, SD)	0.08 ± 0.61	-0.09 ± 1.02	0.09 ± 0.87	0.322	0.561
Short cervix (<25mm)	0 (0)	1 (2.5)	1 (0.8)	0.614	0.478
Scan assessment during the 3rd trimester of pregnancy					
Gestational age 3rd trimester scan (median, IQR)	31.7 (30.5-33.2)	31.8 (30.6-33.2)	31.7 (30.5-33.2)	0.896	0.965
EFW (g, mean, SD)	1868 (±291)	1944 (±284)	1895 ± (287)	0.389	0.200
EFW centile (mean, SD)	51.0 (±31.0)	56.6 (±32.6)	53.3 (±31.8)	0.593	0.296
SGA fetuses (n, %)	10 (8.3)	3 (7.5)	7 (8.8)	0.815	0.815
Pregnancy and perinatal outcome					
Gestational age delivery (median, IQR)	39.2 (38.1-40.5)	39.1(38.0-40.5)	39.0 (38.1-40.5)	0.934	0.806
Birth Weight (mean, SD)	3334 (±495)	3368 (± 497)	3337 (±515)	0.754	0.922
Birth weight (centile, mean, SD)	50.0 (±27.9)	52.7 (± 28.4)	50.9 (±29.2)	0.744	0.655
SGA (n, %)	10 (8.3)	3 (7.5)	8 (10.0)	0.655	0.350

5-minute Apgar <7 (n, %)	5 (4.1)	2 (5.0)	4 (5.0)	1.000	0.518
Preeclampsia (n, %)	9 (7.5)	4 (10.0)	6 (7.5)	0.640	1.000

Data are shown as median (interquartile range) or number (%).
Endo: Endometriosis; Deep infiltrating endometriosis: DE; Ovarian endometrioma: OE; Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

There was no statistically significant difference in the baseline data within the three study groups. Overall, 160 pregnant women had complete follow-up, as required for being eligible for the study analysis; within this population, 40 (25%) had OE, 40 (25%) had DE, and 80 (50%) had no endometriosis.

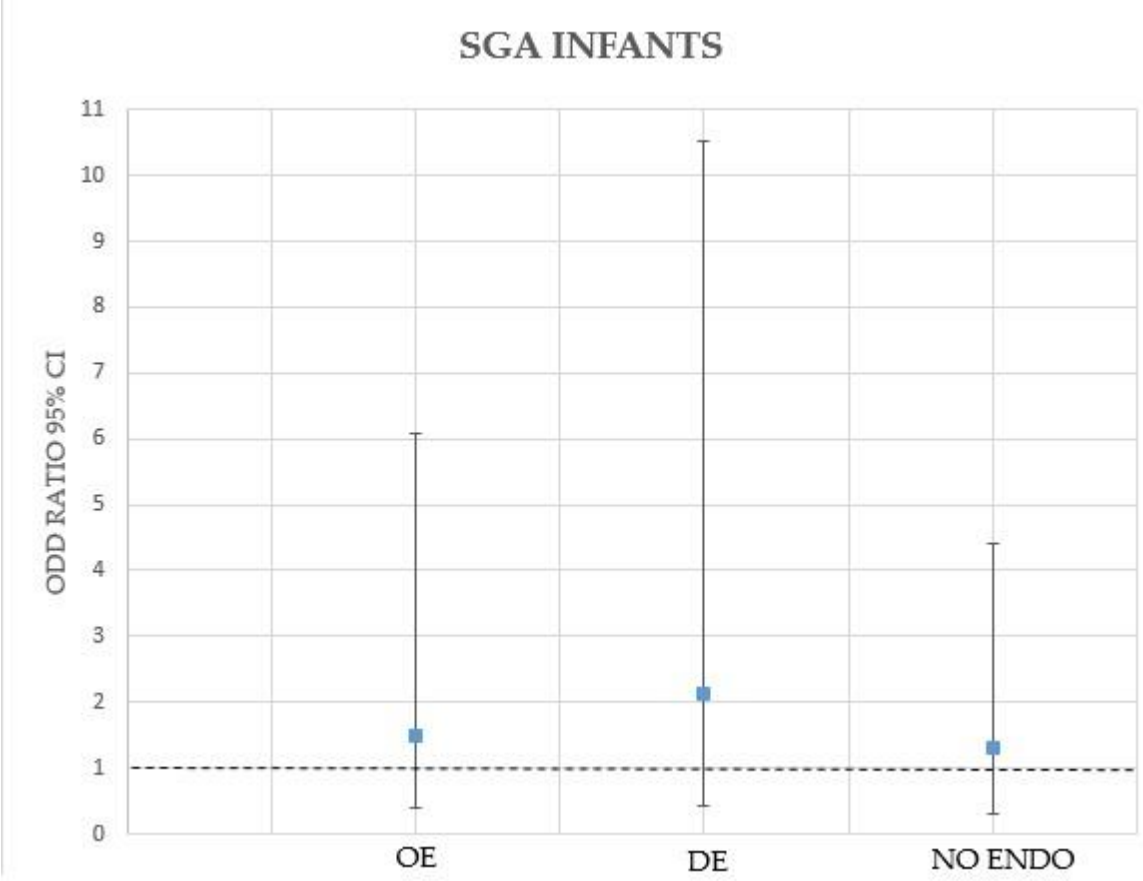
A statistically significant difference was not observed in the first trimester levels of PAPP-A, first trimester and mid-pregnancy mean UtA Doppler PI, EFW centile, and prevalence of SGA fetuses between patients presenting with OE and healthy women; moreover, no statistically significant difference was found in the prevalence of preeclampsia, SGA infants, and five-minute Apgar score between these two groups (Table 1). Moreover, a statistically significant difference was not observed in the first trimester levels of PAPP-A, first trimester and mid-pregnancy mean UtA Doppler PI, EFW centile, and prevalence of SGA infants between patients presenting with DE without OE and healthy women. No statistically significant difference was again found in the prevalence of preeclampsia, SGA infants, and five-minute Apgar score between these two groups (Table 1). The correlation between maternal and pregnancy specific characteristics with SGA and OE and DE was done by logistic regression analysis; Table 2 reports the data related to this analysis. Either the presence of OE nor that of DE without OE were found independently associated with delivering SGA infants (Figure 1).

Table 2. Logistic regression analysis for prediction of SGA

SGA (n)	OR	95% CI	p-value
Maternal age	1.038	0.893-1.207	0.628
BMI	0.977	0.868-1.100	0.704
PAPP-A (MoM)	0.842	0.309-2.296	0.737
UtA mean PI (2nd trimester)	0.359	0.036-3.579	0.383
OE	1.489	0.366-6.067	0.578
DE	2.121	0.426-10.564	0.381

Deep infiltrating endometriosis: DE; Ovarian endometrioma: OE; Body Mass Index: BMI; beta human chorionic gonadotropin: BhCG; pregnancy-associated plasma protein A: PAPP-A; Uterine artery: UtA; Pulsatility index: PI; small for gestational age: SGA

Figure 1. Odds ratios with 95% CIs for delivering SGA infants in women with ovarian endometriomas (OE) and deep endometriosis (DE) in comparison to healthy women (NO ENDO).



DISCUSSION

The results obtained from this study demonstrate that the presence of OE or DE in pregnant women is not associated with an increased risk of delivering SGA infants. During the scan assessment in the

3rd trimester of pregnancy, the prevalence of SGA infants was similar within the three study groups (OE: 8.3%; DE: 7.5%; healthy women: 8.8%); similar results were observed for the prevalence of SGA infants at birth (OE: 8.3%; DE: 7.5%; healthy women: 10.0%). When assessed singularly, conventional risk factors for placental insufficiency, such as BMI, PAPP-A, and mean UtA Doppler PI in first and the second trimesters of pregnancy, did not demonstrate a significant correlation with the presence of OE or DE. More importantly, logistic regression analysis showed that either the presence of OE (1.489; 95 CI % 0.366–6.067; p = 0.578) nor the presence of DE (2.121; 95 CI % 0.426–10.564; p = 0.381) were associated with the occurrence of SGA infants, after adjusting the results for potential confounding variables (maternal age, ethnicity, BMI, PAPP-A, and mean UtA Doppler PI). Thus, these data seem to not support a potential causative link between these endometriotic phenotypes and impaired placentation and subsequent development of SGA births.

According to the existing literature, the relation between endometriosis and adverse obstetrics outcomes, such as preeclampsia and SGA, is still conflicting (11,27). Two recent systematic reviews with meta-analysis tried to summarize evidence on this topic (28,29). In both, subgroup analyses for spontaneous and assisted conception were attempted in order to remove the confounding factor represented by assisted reproduction. In general, women with endometriosis were found to have an increased risk of a range of obstetric and fetal complications, although results for specific adverse maternal and neonatal outcomes tended to differ between these two reviews. Specifically, none of the two (30) reported a pooled increased risk for delivering SGA infants in patients affected by endometriosis; only one (30) observed an increased risk of developing PIH. However, evidence from the analysis of data is limited by the quality and heterogeneity of the studies included: for example, the diagnosis for endometriosis is not uniform; moreover, selection of control groups tends to differ across studies, with some studies evaluating fertile patients, sub fertile patients, or patients a affected by male factor infertility as non-endometriotic controls.

A not negligible number of recent studies have found both lower and unchanged risks for these outcomes. Hadfield et al. evaluated 208,879 women with a singleton first birth in the period 2000–2005 in the Australian state of New South Wales in a large population study; among them, 3239 had an earlier diagnosis of endometriosis. No association between the presence of endometriosis and pregnancy-induced hypertension or preeclampsia was reported in this study (30); notably, stratification for ART did not change the results. In another observational study, Benaglia et al. reported an unchanged risk of hypertensive disorders, preterm birth, gestational diabetes, SGA and large for gestational age newborns, and neonatal problems in women affected by endometriosis (15). Otherwise, Stephansson et al., in a large cohort of women affected by this chronic benign disease, found an increased risk of pre-eclampsia, preterm birth, antepartum bleeding/placental complications, and cesarean section, but any statistically significant association with SGA infants or stillbirth was not found (14).

Recently, our academic group demonstrated that the presence of di use adenomyosis in pregnant women affected by endometriosis is strongly associated with SGA infants, thus suggesting a causative relationship between di use adenomyosis and placental dysfunction (18).

The current study investigated, for the first time in the literature, the influence of OE and DE without OE on adverse pregnancy outcomes in women who conceived spontaneously, revealing that neither the presence of OE nor that of DE alone should not be considered relevant risk factors for placental impairment and consequently delivering SGA infants. This study is characterized by some limitations: firstly, its design is retrospective, although the data were prospectively collected. Furthermore, its sample size is relatively small and this could be considered an impediment for definite conclusions, especially when performing subgroup analysis.

However, the study population was highly selected, being composed of women with endometriosis who spontaneously conceived. Given that the main aim of the study was to give information for clinical practice, we were interested in associations of relevant size; in the near future, these preliminary findings may pave the way for trials with larger sample sizes. A further limitation of the current study is that the presence of specific localizations of endometriosis was assessed before conception by ultrasonography. Ideally, a diagnostic laparoscopy before conception would provide a better assessment of the disease but obviously, it is not ethically acceptable to perform a surgical procedure only for this purpose; anyway, because of this study design, we were not able to determinate whether some patients with OE had small DE lesions (main diameter less than 1 cm) not detected by ultrasonography; in contrast, it seems unlikely that OEs were not diagnosed by ultrasonography in the DE group. Similarly, the presence of superficial peritoneal endometriosis in the control group cannot be excluded. However, considering that endometriosis has a low prevalence (about 4%) in the general population (1) and that the control patients did not have pain symptoms requiring antalgic therapy prior to conception, it seems unlikely that a relevant percentage of control women had undiagnosed endometriosis.

A strength of this observational study is that patients with OE and DE without OE were separately studied in subgroups and compared to women without endometriosis; this has been done in order to better understand the impact of each phenotype of endometriosis on specific adverse pregnancy outcomes, and in particular on delivering SGA infants. Moreover, patients who conceived by ART procedures were excluded, thus eliminating the potential bias related to higher prevalence of adverse pregnancy outcomes, such as in cases of preeclampsia.

CONCLUSIONS

The current study shows that the presence of OE and DE without OE are not risk factors of delivering an SGA infant. Thus, patients affected by endometriosis should be treated during pregnancy as the general population, not needing closer monitoring.

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CHAPTER 6 CLASSIFICATION OF FGR

Normal fetal growth reflects the interaction between genetically pre-determined growth potential and fetal, placental, and maternal health. Normal fetal growth has a primary phase of cellular hyperplasia in the first 16 weeks of the pregnancy. Between 16 and 32 weeks, there is a concomitant phase of hyperplasia and cellular hypertrophy, with an increase in the number and size of cells. From week 32, there is a cellular hypertrophy phase, with a rapid increase in cell size. This pattern of normal fetal growth is the basis for the clinical classification of FGR.

Campbell (1) used the head circumference/abdominal circumference (HC/AC) ratio to differentiate between symmetrical or harmonic small fetuses and asymmetrical fetuses, i.e., those with a disproportionately slower growth of AC, and classified FGR into types I, II, and III.

Type I: this type include FGR fetuses with a symmetrical harmonic restricted growth, defined by a reduced intrinsic potential of growth. These fetuses shows a proportional decrease in the size of both head and abdomen circumference. Etiological factors affect the growth pattern of these fetuses at an early stage, during the cellular hyperplasia phase.

Type II: this type is characterized by a late onset of drop in growth, after 30 or 32 weeks, in the cellular hypertrophy phase, generally resulting in asymmetry and disharmony. HC and FL are less affected, corresponding to the gestational age. However, AC is commonly most seriously affected, decreasing the estimated fetal weight. The main etiological factor of asymmetric FGR is placental insufficiency.

Type III: this type results from an association of the previous two mechanisms (types I and II). The change occurs in the second trimester, which is when the hyperplasia and hypertrophy phases occur. Since the changes occurs at a relatively early stage of pregnancy, the fetuses show semi harmonious growth with a hypotrophic appearance. It is usually due to embryonic infections such

as those caused by rubella virus, cytomegalovirus, and Toxoplasma gondii as well as with toxic agents that affect the fetus, such as pharmaceuticals, illegal drugs, and toxins.

Nowadays, the chronological classification of FGR, which is based on the time of onset, is the most commonly used classification. This new classification has a better clinical applicability helping clinician in the management of the FGR fetuses. Figueras and Gratacós (2) and Baschat (3) have reported different pathophysiological behaviors in fetuses with FGR before and after 32 weeks. Fetuses with early FGR (<32 weeks) showed a substantial change in placental implantation, which often leads to increased resistance in the uterine artery and an increased risk of developing PIH and preeclampsia. For this reason, the risk of fetal hypoxia is higher and fetuses usually present cardiovascular adaptation. Perinatal morbidity and mortality rates are high. In late-onset FGR (≥32 weeks), there are slight placentation deficiencies that lead to mild hypoxia and require little cardiovascular adaptation by the fetus. However, the degree of tolerance to hypoxia is low; in contrast to cases of early onset FGR, the fetus are not able to tolerate this low oxygen supply for long. The major challenge in early onset FGR is management, while the problem associated with late-onset FGR is early diagnosis, because the umbilical artery Doppler findings may still be normal, thereby masking the disease.

In 2016, has been proposed the Delphi procedure to define, classify and diagnose FGR fetuses (4). During this consensus the 32nd week of gestation was defined as the cut-off point for early versus late-onset FGR classification, and fetuses with congenital anomalies were excluded from this classification. Thus, in early onset FGR, the estimated fetal weight and/or AC is less than the third percentile or the umbilical artery Doppler which shows absent and/or zero diastolic flow. Early onset FGR can also be classified and diagnosed when two of the following three parameters are present: (1) estimated fetal weight and/or AC < the tenth percentile, (2) pulsatility index (PI) of the uterine artery > the 95th percentile, and (3) PI of the umbilical artery > the 95th percentile. Late-onset FGR

is determined by only one parameter: estimated fetal weight and/or AC < the third percentile. Late-onset FGR can also be classified and diagnosed when two of the following three parameters are present: (1) estimated fetal weight and/or AC < the tenth percentile, (2) fetal growth two “quartiles” lower during fetus monitoring, and (3) cerebroplacental ratio (CPR) < the fifth percentile. Doppler follow-up of the umbilical artery has a major importance in early onset FGR. In cases of late-onset FGR, umbilical artery Doppler can be normal or only become abnormal in advanced stages of the disease. In late-onset FGR, placental dysfunction is less severe and we can observe decreasing of middle cerebral artery Doppler and cerebral placental ratio (CPR) with normal or minimal uterine artery Doppler abnormalities.

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CHAPTER 7 DOPPLER VELOCIMETRY

The Doppler velocimetry assessment enables the non-invasive detection of signs of placental insufficiency and of fetal hemodynamic changes that occur during fetal cardiovascular adaptation. The Doppler velocimetry assessment can be performed using the uterine arteries (maternal circulation), umbilical arteries (feto-placental circulation), and other fetal vessels [cerebral artery, abdominal aorta, renal artery, ductus venosus (DV), and transverse sinus]. This analysis is fundamental to identify restricted fetuses at risk of hypoxia, which occurs in approximately 40% of cases (1). Moreover, it is helpful to make a differential diagnosis of pathological restrictions, i.e., between fetuses that are deficient in nutrients or have hypoxia and require intensive management and those that are constitutionally small, in which case, a more conservative treatment can be adopted.

CHAPTER 7.1 Uterine artery Doppler

The uterine artery Doppler evaluation plays a key role in the diagnosis of abnormal placentation. It has been assessed in a previous study the role of uterine artery evaluation between 11 and 14 weeks, particularly for the prediction of pre-eclampsia, usually associated with early onset FGR. The authors used the mean PI uterine artery Doppler as parameter using a cutoff >2.35 (sensitivity for isolated prediction of FGR and needed for delivery <32 weeks due FGR of 11.7 and 27.8%, respectively) (2). It can also be re-evaluated during the second trimester, because it identifies pregnancies with a risk of placental failure, pre-eclampsia, and SGA through increased resistance (mean PI uterine artery > 95th centile) with or without the presence of unilateral or bilateral diastolic notch (3).

A recent consensus established the importance of fetal evaluation using a uterine artery Doppler, particularly in cases of early onset FGR. PI of the uterine arteries > the 95th percentile associated with estimated fetal weight or with AC < the 10th percentile represents a sufficient parameter for FGR diagnosis (4).

CHAPTER 7.2 Umbilical artery, medial cerebral artery, and fetal hemodynamic centralization

The umbilical artery Doppler reflects placental vascular resistance, which is strongly correlated with placental impairment. In a normally grown fetus, umbilical artery resistance gradually decreases during pregnancy, while in case of FGR, particularly in early onset FGR, the reverse occurs (5). The reduction in placental flow is the first hemodynamic signal of a placental lesion, with impaired villi microcirculation (6). Thus, placental lesions are associated with a decrease in umbilical artery perfusion, increasing PI and RI uterine artery Doppler values (Figure METTI IMMAGINI DOPPLER PATOLOGICO).

The next step in fetal deterioration in response to placental insufficiency is the hemodynamic centralization. During hypoxemia, there is selective vasodilation to preserve major organs, particularly brain, heart, and adrenals glands and a contemporaneous vasoconstriction in other organs (the kidney, lung, intestine, skin, and bones) (7).

Thus, the fetal hemodynamic centralization process worsens umbilical artery PI, with a loss of its diastolic component until it becomes inverse, in addition to increasing the resistance in the distal thoracic aorta with a higher PI.

Next, the ratio between PI of the middle cerebral artery and the umbilical artery becomes progressively smaller because of cerebral vasodilation, determined by the decrease in PI of the medial cerebral artery.

Ductus venosus (DV) plays an fundamental role in delaying the fetal hemodynamic centralization process by redirecting a significant amount of blood flow from the fetal liver to the heart, thereby ensuring more blood flow to the heart and brain (8).

The increase in DV flow is allowed by two factors: the existence of innervation and that of musculature in the anastomosis of the umbilical vein in the hepatic portal system, leading to the enlargement of DV and increase in resistance in the right hepatic vein (9).

It has been observed that the occurrence of decelerations in antepartum cardiotocography has a 2-week delay between the onset of fetal hemodynamic centralization. Therefore, it can be concluded that Doppler abnormalities precede changes in the biophysical profile.

The disappearance of the diastolic component on the umbilical artery Doppler coincides with changes in the acid–base balance (10, 11). Perinatal mortality is higher in this group, with several neonatal complications due to vasoconstriction in several organs (10).

Preceding fetal death, there is generalized vasoplegia and irreversible hemodynamic changes, a period referred to as flow decentralization (12). Cerebral edema is the result of the accumulation of lactic acid during the period of hypoxia and anaerobic respiration, altering cell membrane permeability and increasing intracellular osmotic pressure with the appearance of necrosis and edema (13). Because of edema, difficulty in cerebral perfusion occurs, with the appearance of highly resistant flow rate waves on the Doppler of the medial cerebral arteries, even without the diastolic component. Concomitantly, changes in the umbilical area persist, and in some cases, a false normalization of this area may occur, while persistent changes in the venous system persist.

CHAPTER 7.3 CPR

CPR, calculated as the product of PI of the medial cerebral artery and PI of the umbilical artery is another tool to assist assessment and management of FGR. Abnormal CPR has recently been associated with adverse perinatal outcomes, higher admission rates in intensive care units (NICUs), post-natal neurological deficits, and lower Apgar scores.

Recently DeVore (14) reviewed several studies in which CPR was assessed in both normal and SGA fetuses to determine whether the test should be conducted in clinical practice. What has been found was that an abnormal CPR was a better predictor of adverse events than the biophysical profile in cases of early onset FGR. Moreover, in normal for gestational age fetuses, an abnormal CPR could predict fetal distress during labor.

The high specificity of CPR could help in the selection of fetuses at risk that require closer monitoring.

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CHAPTER 8 STUDY 3:

Mid pregnancy fetal growth, uteroplacental doppler indices and maternal demographic characteristics: role in prediction of stillbirth

INTRODUCTION

The birth of a stillborn infant is a devastating outcome of pregnancy and unfortunately is still a relatively common occurrence (1,2). Although several maternal and obstetric characteristics are associated with the risk of stillbirth, they explain less than 20% of the variance in the incidence of stillbirth and the major risk factor recognized for intrauterine death (IUD) is placental insufficiency (3-5). While two-thirds of stillbirths are "unexplained" by conventional classification, fetal growth restriction resulting from placental insufficiency is present in over half of these cases despite an apparently appropriate birthweight for gestational age (AGA) (6,7). Indeed, neonates defined as AGA may not have achieved their true growth potential leading to an incorrect classification that are likely to account for the group of stillbirth classified as unexplained on the basis of fetal size rather than Doppler criteria. Uterine artery (UtA) Doppler assessment has a strong association with impaired placental function (8) and several publications have reported the association of abnormal uterine artery Doppler indices both in the first and second trimester to stillbirth even when apparently unexplained (6,9-11). Several biophysical and biochemical tests performed during the first two trimesters of pregnancy have been proposed to predict stillbirth (5,9,11-13) but to date, there is still no clinically useful first or second- trimester test to predict IUD in unselected pregnant women. The aim of this study was to investigate the potential value of screening integrating mid-pregnancy maternal demographics, fetal biometry and UtA pulsatility index (PI) in prediction of IUD and to examine the potential value of such assessment in identifying women who may benefit from

increased antenatal surveillance. The ability to predict stillbirths early in pregnancy and to offer additional surveillance and intervention to high-risk mother/fetus is understandably an important part of antenatal care.

MATERIAL AND METHODS

This was a retrospective cohort study of data obtained in a single maternity center over a 14-year period from 2000 to 2014. Inclusion criteria were: singleton pregnancy morphologically normal attending their routine scheduled ultrasound examination between 19 and 24 weeks of gestation. As a retrospective study of routinely collected data, ethics approval was not required (as for NHS-REC). Secondly, the ethics committee approved the collection of pregnancy outcome data as part of the routine follow-up of FMU patients. Pregnancies complicated by fetal abnormality, maternal medical disorders, previous adverse obstetric outcome, aneuploidy or infection were excluded from the analysis. In addition, all patients that delivered elsewhere or referred from other hospitals were excluded from the study as it was not possible to obtain the postnatal outcomes. Gestational age (GA) was determined according to crown–rump length (CRL) in the first trimester (13). All the patients underwent a nuchal scan and double test as for the first trimester NHS protocol and only those classified as low risk have been included in the study. Data on ultrasound examinations were obtained from computerized records (Viewpoint software, General Electric, Wauwatosa, WI, USA) and only one (the anomaly scan) examination per fetus was included in the analysis. Ultrasound examinations were performed mainly with a Voluson GE (GE Medical Systems, Zipf Austria) ultrasound machine equipped with a 2-8 MHz convex probe. Qualified and experienced sonographers performed all scans. Maternal characteristics recorded included maternal age, body mass index, parity, ethnicity (Caucasian, Afro-caribbean, Asian and mixed), medical history and obstetric history. Data on pregnancy outcomes were collected from the hospital maternity records.

Ultrasound data, including head circumference, abdominal circumference and femur length (FL), were measured according to a standard protocol (15) and were converted to percentiles using reference values derived from low-risk pregnancies with documented normal outcome. Transabdominal color Doppler ultrasound was used to visualize the uterine arteries at the apparent crossover with the external iliac arteries (14). Measurements were taken with pulsed- wave Doppler at the lowest insonation angle achievable and when uniform waveforms with high signal to noise ratio were obtained the PI was measured. Maternal characteristics, second-trimester fetal biometry and Doppler measurements were compared between women who delivered stillborn and those who delivered live born babies. Maternal age, body mass index and all the ultrasound parameters were included as continuous variables; parity and ethnicity as nominal variables.

Stillbirth was defined as the death of a fetus with a birthweight≥ 500 g or a gestational age >23+6 weeks of gestation (1). We compared the potential value of maternal characteristics, fetal biometry and UtA Doppler indices in prediction of preterm and term stillbirths defining two groups: term stillbirth occurring > 37 weeks' gestation and preterm stillbirth occurring at < 37 weeks' gestation.

Multivariate logistic regression analysis was used to estimate the association between second-trimester ultrasound measurements and stillbirth and to determine the independence and relative contribution of variables. All variables significantly associated with stillbirth were included in the model. The risk for each of the pregnancy outcomes was then calculated from the formula: odds/(1+odds), where odds=e^{Y}, and Y was derived from the multivariate logistic regression analysis. The performance of screening was determined by receiver operating characteristic (ROC) curves. SPSS version 20 (SPSS Inc, Chicago, IL) was used for statistical analysis, and a p-value<0.05 was considered significant.

RESULTS

The study included 23,894 pregnancies that were scanned between 19 and 24 weeks' gestation (Table 1). There were 90 stillbirths after 24 weeks' gestation: 38 stillbirths occurred at term and 52 were preterm. The results of the multivariate regression of the association between maternal characteristics and ultrasound parameters and the risk of stillbirth are shown in Table 2. Non-Caucasian ethnicity, FL centile and UtA PI were significantly associated with the risk of stillbirth (all $p < 0.01$). The ROC curves of second trimester maternal demographics, fetal biometry and UtA Doppler parameters for predicting all, term and preterm stillbirths are presented in Figure 1 and Figure 2. The area under curve (AUC), the detection rates (DR) at a various false positive rates (FPR) of screening by maternal demographics, fetal biometry, UtA PI and their combination for stillbirth are given in Table 3.

Screening by maternal demographics alone - at a 10% FPR – had a DR of 12% and 14% for term and preterm stillbirths, respectively. Screening combining maternal demographic characteristics, FL centile and UtA Doppler indices at the same FPR had a DR of 31 % for prediction for all stillbirths. In the term population, the DRs at 10% FPR were 27%, 24% and 27% using the combined parameters, UtA Doppler indices alone and FL centile in isolation, respectively.

In addition, a sub-analysis was performed stratifying the results by Caucasian and non- Caucasian ethnicity (Supporting Information Table S1). No statistically significant differences were found comparing the AUCs and the DRs between these two groups (Supporting Information Table S1).

Table 1 Baseline demographics of the study population . Data are given as mean ± SD or n (%). Small-for gestational age, SGA.

Characteristic	***Population (=23804)***	***Stillbirths (=90)***	***P value***
Maternal age (years)	29.99 ± 5.6	30.6 ± 6.6	**0.021**
BMI (kg/m2)	24.55 ± 4.8	25.24 ± 5.1	0.062
Ethnicity			
• Caucasian • Asian • Afro-caribbean • Mixed-others	13401 (56.3%) 4942 (20.8%) 3501 (14.7%) 1960 (8.2%)	51 (56.8%) 13 (14.4%) 13 (14.4%) 13 (14.4%)	0.940 **0.039** 0.078 **0.033**
Gestation age at scan (weeks)	21.8 ± 0.6	21.9 ± 0.6	0.630
Gestational age at delivery (weeks)	39.7 ± 2	35.4 ± 4	**0.000**
HC centile	58.81 ± 22.6	55.74 ± 24.1	0.146
AC centile	59.42 ± 21.09	53.75 ± 25.37	**0.003**
FL centile	59.83 ± 22.70	50.12 ± 27.46	**0.001**
Ut A Doppler PI	0.875 ± 0.55	1.09 ± 0.72	**0.000**
BW (g)	3295.6 ± 578	2508 ± 824	**0.000**
Term delivery	22,241 (93.4%)	38 (42.2%)	**0.000**
Preterm delivery <37 weeks	1,563 (6.6%)	52 (57.8%)	**0.000**
Preterm delivery < 32 weeks	291 (1.2%)	25 (27.8%)	**0.000**
SGA	2908 (12.2%)	35 (38.9%)	**0.000**

Table 2. Results of the multivariate logistic regression analysis of factors associated with Stillbirth

Maternal demographics, fetal biometry and Dopplers	***Unadjusted Odds Ratio***	***Adjusted Odds Ratio***	***95% Confidence Interval***	***P value***
BMI	1.027	1.021	0.98-1.10	0.189
Age	1.016	1.013	0.95-1.07	0.776
Ethnicity				
• Caucasian	0.674	0.680	0.41-1.07	0.063
• Asian	1.457	1.303	1.22-1.45	**0.015**
• Afro-caribbean	1.234	1.146	0.97-1.33	0.079
• Mixed-others	2.3	2.574	1.18-5.58	**0.017**
AC centile	0.993	0.988	0.98-1.01	0.184
FL centile	0.986	0.982	0.98-0.99	**0.003**
HC centile	1.003	0.994	0.99-1.01	0.615
UtA PI (sum)	2.107	2.249	1.67-2.65	**0.000**

Table 3. Performance of screening for all, term, preterm and very preterm stillbirths with maternal demographics, FL centile and UtA Dopplers.

SCREENING TEST	AUC	DR at 10% FPR	DR at 20% FPR	DR at 30% FPR	DR at 40% FPR
All Stillbirths					
Maternal demographics	0.568	19%	34%	45%	50%
FL centile	0.601	26%	37%	47%	53%
UtA Dopplers	0.693	28%	50%	62%	72%
Mat demographics + FL+ UtA PI	0.717	31%	46%	61%	72%
Term Stillbirths					
Maternal demographics	0.574	12%	19%	29%	36%
FL centile	0.595	27%	37%	50%	53%
UtA Dopplers	0.682	24%	45%	60%	74%
Mat demographics + FL+ UtA PI	0.714	27%	37%	47%	53%
Preterm Stillbirths					
Maternal demographics	0.556	14%	23%	38%	54%
FL centile	0.615	23%	36%	44%	54%
UtA Dopplers	0.705	31%	50%	62%	71%
Mat demographics + FL+ UtA PI	0.722	35%	44%	62%	75%
Very preterm Stillbirths					
Maternal demographics	0.583	12%	20%	29%	38%
FL centile	0.598	28%	36%	50%	52%
UtA Dopplers	0.761	40%	56%	72%	80%
Mat demographics + FL+ UtA PI	0.768	40%	53%	60%	78%

DISCUSSION

This screening study evaluated the role of mid pregnancy maternal demographics, fetal biometry and UtA Doppler indices, alone or in combination, in prediction of stillbirth in a large population of low-risk women attending for routine care at 19-24 weeks of gestation. The findings of the study demonstrate that the second trimester assessment does not achieve a high performance in detecting term stillbirths and this is consistent with the current available literature (9-16). On the other hand, the performance improved to a sensitivity of 35% for a 10% FPR when examining the rate of preterm stillbirths. Preterm stillbirths show a strong association with severe intrauterine growth restriction (IUGR) explaining why the UtA Doppler indices are the best single predictor (9). Moreover, this study shows of the fetal biometry parameters, only the FL centile was an independent predictor of IUD in our population of low risk woman. The performance of the screening for detection of stillbirth was only marginally improved by the addition of FL to the UtA Doppler assessment as showed by ROC curves (Figure 1 and 2). In contrast, second trimester assessment performed better than the use of maternal demographic characteristics and risk factors as is conventional in clinical practice currently. These discordant findings for gestation of stillbirth could be explained either because term stillbirth has a different aetiology or because the interval between the assessment and the time of the stillbirth affects the performance of the screening. The major strengths of our study include the large number of pregnancies attending for routine assessment at 19-24 weeks of gestation, adjusting for possible confounding variables and ascertainment of the outcome data. The retrospective design is a limitation and the data could be biased by selective assessment of a high risk population based on the availability of UtA Doppler indices results to the obstetricians.

Several biophysical and biochemical tests performed during the first two trimesters of pregnancy have been proposed to predict stillbirth (5,9,11) but to date, there is still no clinically useful first or

second-trimester test to predict IUD as a sole category in unselected pregnant women. Studies over the past two decades have confirmed UtA Doppler as potentially useful in predicting pregnancies at high risk of developing complications related to utero-placental insufficiency (9,11,16). Smith et al. (9) showed that UtA Doppler at 22-24 weeks' gestation in a population of low risk unselected women is associated with increased risk of all causes of stillbirth up to 32 weeks (sensitivity 58% for a FPR of 5%); conversely the prediction at later gestational age was poor with a sensitivity of 7% at the same FPR. However, fetal biometry was not included in the analysis and the results of our study interestingly show an independent contribution of FL measurement in prediction of stillbirth. In high risk women, the use of UtA Doppler indices showed a better performance in predicting stillbirth at term (6). The explanation of this difference can be identified in the increased prevalence of stillbirth in the high risk population and the influence of intervention bias as abnormal results were revealed to clinicians who may have modified the management of the pregnancy (6).

A recent systematic review and meta-analysis (11) showed that serum levels of pregnancy-associated plasma protein A (PAPP-A) in the first trimester and UtA PI in the second trimester have a high predictive accuracy for stillbirth related to placental dysfunction and pointed out the impact that the introduction of such tests could have in reducing the risk of placental dysfunction-related stillbirth. Evidence suggests that the detection of a FL below the expected value (< 5th centile) at mid-trimester ultrasound examination is a feature of IUGR (17- 19). Weisz et al. (19) showed in a large cohort that 20% of cases of isolated short femur in the second trimester were associated with subsequently diagnosed IUGR and lower levels of PAPP- A. However, this study did not incorporate Doppler analysis. The aetiology of femur shortening in IUGR fetuses is unclear. A study of body proportionality of small for gestational age fetuses found that in most cases of small for gestational age due to abnormal placentation, the reduced FL was concordant with the small abdominal circumference (20). Another study (21) speculated that abnormal placentation altered the level of

fibroblast growth factor receptor-2, resulting in growth restriction of the fetal long bones and this can account for the finding of isolated short femur in pregnancies with impaired placental function. The well-accepted hypothesis that stillbirth is related to multiple aetiologies and not to a single disorder makes it unlikely that any single test will be able to predict all-cause stillbirth. The most avoidable cause of stillbirth is certainly the one related to an impaired placental function defined as IUGR rather than the one based on birth weight-criteria. The results of our study show that a high resistance pattern of flow in the UtA in the second trimester is associated with an increased risk of stillbirth and that this association is strongest for stillbirths due to placental dysfunction. While consistent with other studies, the current comprehensive evaluation of mid pregnancy maternal demographics, fetal biometry and UtA Doppler provides evidence that other factors have a relative importance for prediction of placental stillbirths such as the finding of shortening of FL. The clinical custom of using fetal size as an indicator of adverse outcome makes it difficult to identify placental insufficiency near term in a fetus of normal weight. Indeed placental insufficiency can result from an abnormal placental development – leading to the early onset fetal growth restriction. Alternatively, placental dysfunction may occur because a normally formed placenta is unable to cope with the higher fetal metabolic demands as may occur at term with a normal or increased fetal size (22). This could explain why the second trimester screening using UtA Doppler indices does not achieve a performance good enough in identifying this subset of patients as “high-risk” of term stillbirth and suggest that a third trimester assessment might be required. In this scenario it becomes a priority to recognize criteria directly related to placental function rather than fetal weight population definitions in order to reduce the rate of “unexplained” stillbirth by correctly classifying the placental stillbirths. This information may be useful to improve pregnancy outcome by increased surveillance and timely intervention. Future studies will be needed to investigate the potential

benefit of scheduling further scans and Doppler evaluation for the selected “high risk” pregnancies to improve performance in the prediction of pregnancy outcomes.

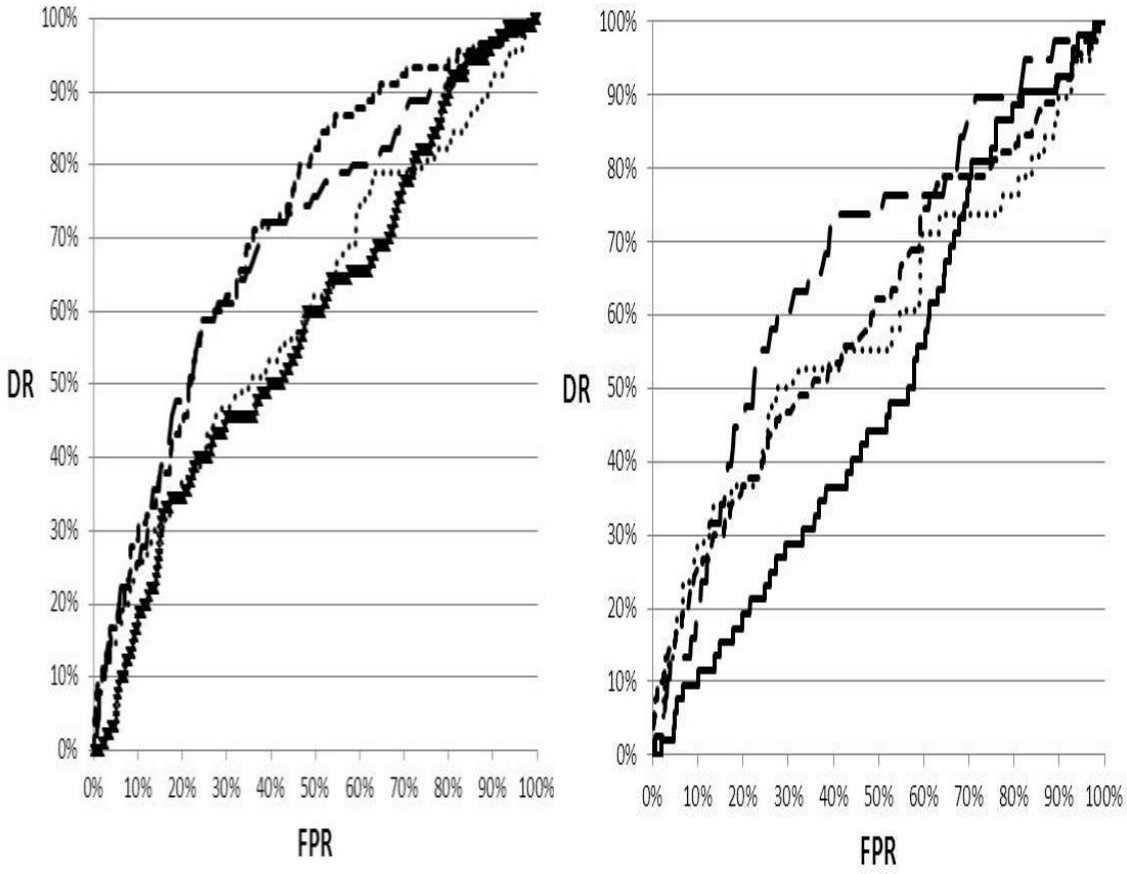

Fig.1 : Receiver operating characteristic (ROC) curves for screening by maternal demographics (smooth black line), Fl centile (round dot line), UtA Doppler PI (dash line) and maternal factors, FL centile and UtA Doppler PI (square dot line) in the prediction of all stillbirths (left)

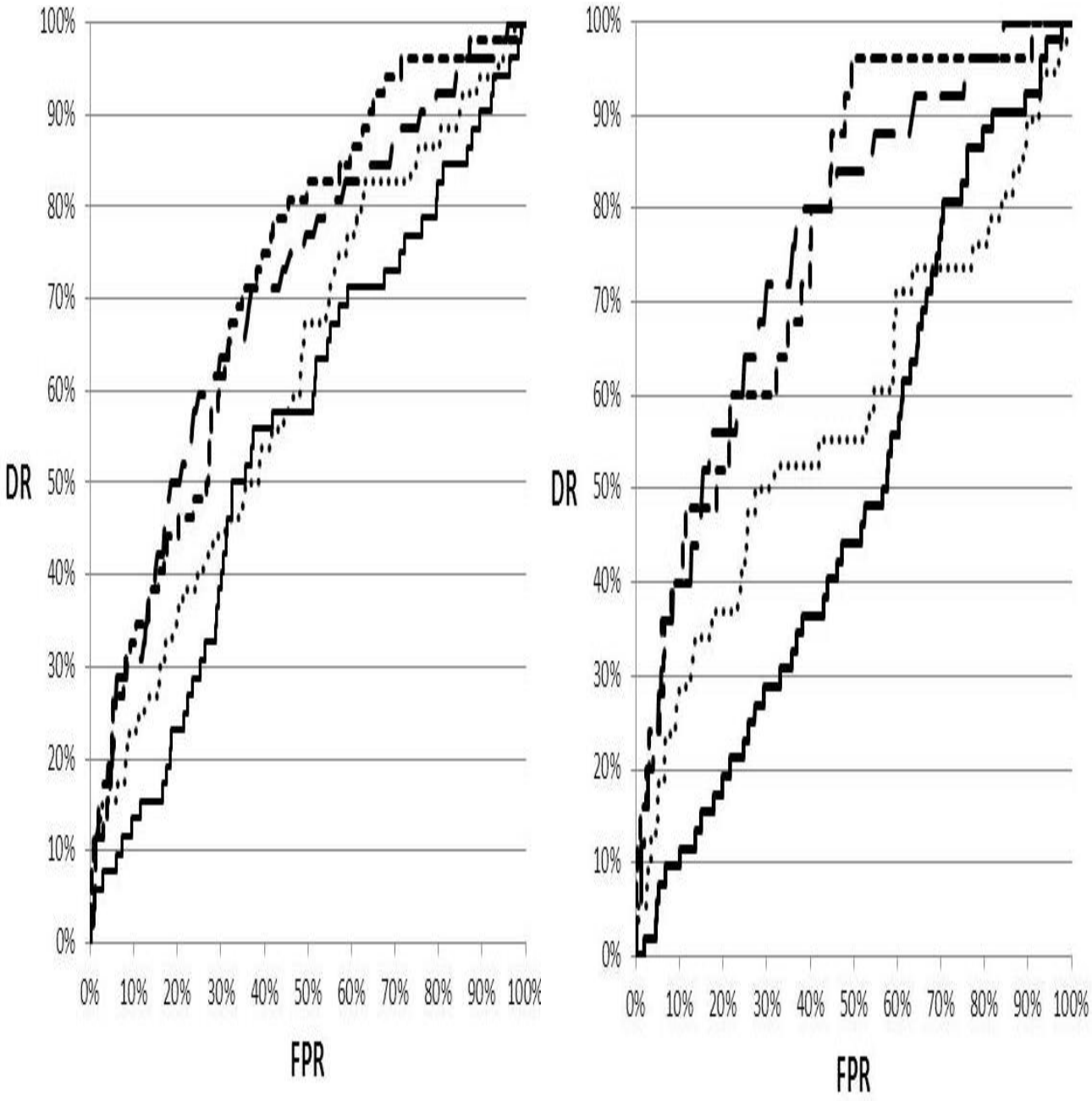

Fig.2 : Receiver operating characteristic (ROC) curves for screening by maternal demographics (smooth black line), Fl centile (round dot line), UtA Doppler PI (dash line) and maternal factors, FL centile and UtA Doppler PI (square dot line) in the prediction of preterm (< 37 weeks' gestation) (left) and very preterm (< 32 weeks' gestation) stillbirths (right).

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CHAPTER 9 MANAGEMENT OF FGR

The main strategies in the management of FGR fetuses is the evaluation of fetal wellbeing and vitality and the subsequent decision regarding when delivery should take place (1).

Several studies in the las years focused their attention to identify the correct management of these fetuses. “The Growth Restriction Intervention Trial (GRIT)” randomly classified women with FGR fetuses between 24 and 36 weeks of gestation in two different groups: immediate delivery and expectant management. Of these patients, 40% had zero or reversed diastolic flow on the umbilical artery Doppler. The immediate delivery group had fewer stillbirths (2 versus 9 in the expectant group); however, it had more neonatal and infant deaths (27 versus 18), particularly in patients with gestations <31 weeks (2). The 13-year follow-up of children showed no differences between groups in terms of cognition, language skills, motor skills, or behavioral development (3). These data suggest that expectant management of very premature restricted fetuses, when there are questions about the time of delivery, will result in some fetal deaths, but immediate delivery results in a similar number of neonatal deaths. Neither of the two methods produced a better neurological outcome.

In the “TRUFFLE: A trial of umbilical and fetal randomized flow in Europe” study, neurodevelopmental outcome was assessed at 2 years after delivery for cases of fetuses with early onset FGR born before 32 weeks. Fetuses were divided into three groups on the basis of the delivery time and different fetal wellbeing assessment strategies: group 1 reducing the short-term variation in computerized cardiotocography; Group 2 early changes in DV (95th percentile), and Group 3 late changes in the DV (zero wave). Most deliveries were recommended for reasons other than changes that recommended delivery in each group. The groups that were based on the DV Doppler used cardiotocography as a safety criterion, whereas in the cardiotocography group, a safety criterion was not applied to the DV Doppler. The hypothesis was that a slight worsening in the prognosis of

the cardiotocography group could be explained by the lack of information from the DV Doppler. Therefore, the authors concluded that to optimize the decision regarding the time of delivery in cases of early onset FGR, fetuses should be monitored longitudinally using a DV Doppler and computerized cardiotocography (4).

The objective of a clinical protocol for the management of FGR is to combine the existing evidence on various assessment of fetal wellbeing (cardiotocography, biophysical profile, and Doppler) to achieve better growth and lung maturity and minimize the risk of morbidity as well as fetal and neonatal mortality. This decision is often based on the gestational age, etiology of growth restriction, extent to which the fetus is compromised, and experience and technological resources available for the evaluation of the fetus and for neonatal treatment. The delivery should be preferably performed in a tertiary hospital.

CHAPTER *9.1 Management of SGA fetuses*

Fetal wellbeing with doppler velocimetry and biophysical profile and growth should be performed every 2 weeks. If the patient does not go into labor spontaneously, labor may be induced at 40 weeks. It is recommended to avoid the use of prostaglandins in the induction of labor because of the risk of hyperstimulation in fetuses that may have some degree of placental injury (5).

CHAPTER *9.2 Management of FGR fetuses with normal Doppler)*

Fetal wellbeing with doppler velocimetry and biophysical profile and growth should be performed every week for fetuses in which the estimated fetal weight is below the third percentile without Doppler anomalies. Birth may be induced around 38 weeks, but the use of prostaglandins should be avoided (5). If the estimated weight percentile is less than 1, delivery should be considered at 37 weeks.

CHAPTER *9.3 Management of FGR with moderate placental insufficiency (with Doppler changes, Stage I)*

In case of the presence of umbilical artery PI > the 95th percentile with positive EDF, median cerebral artery PI < the fifth percentile, or CPR < the fifth percentile on the Doppler, the evaluation of fetal wellbeing is recommended every week.

The induction of birth at 37 weeks is acceptable, but the use of prostaglandins should be avoided. Furthermore, there is also the risk of intrapartum fetal distress (6). If it is not possible rigorous fetal monitoring or there is suspected or abnormal test, CTG or biophysical profile, delivery should be considered between 34 and 37 weeks of gestation to avoid adverse perinatal outcome.

CHAPTER *9.4 Management of FGR with severe placental insufficiency (Doppler of the umbilical artery with zero diastolic flow, Stage II)*

FGR fetuses with zero diastolic flow on the umbilical artery Doppler or reversed diastolic flow, needs to be monitored every 2 or 3 days [4]. Delivery at 34 weeks, usually by the elective cesarean section, is recommended, because the risk of fetal distress in labor induction exceeds 50% (5).

CHAPTER *9.5 Management of FGR with advanced fetal deterioration (umbilical artery Doppler with reversed diastolic flow or DV with pi > 95th percentile, Stage III)*

In case of the presence of reversed diastolic flow on the umbilical artery Doppler or PI > the 95th percentile on the DV Doppler, there is a high risk of fetal death and impaired neurological

development. Hospitalization and daily fetal monitoring (Doppler and cardiotocography) are recommended. Delivery is recommended at 30 weeks (5).

CHAPTER *9.6 Management of FGR with high probability of fetal acidosis and high risk of fetal death (Doppler of DV with reversed wave, computerized cardiotocography <3 ms, or decreased fetal heart rate, Stage IV)*

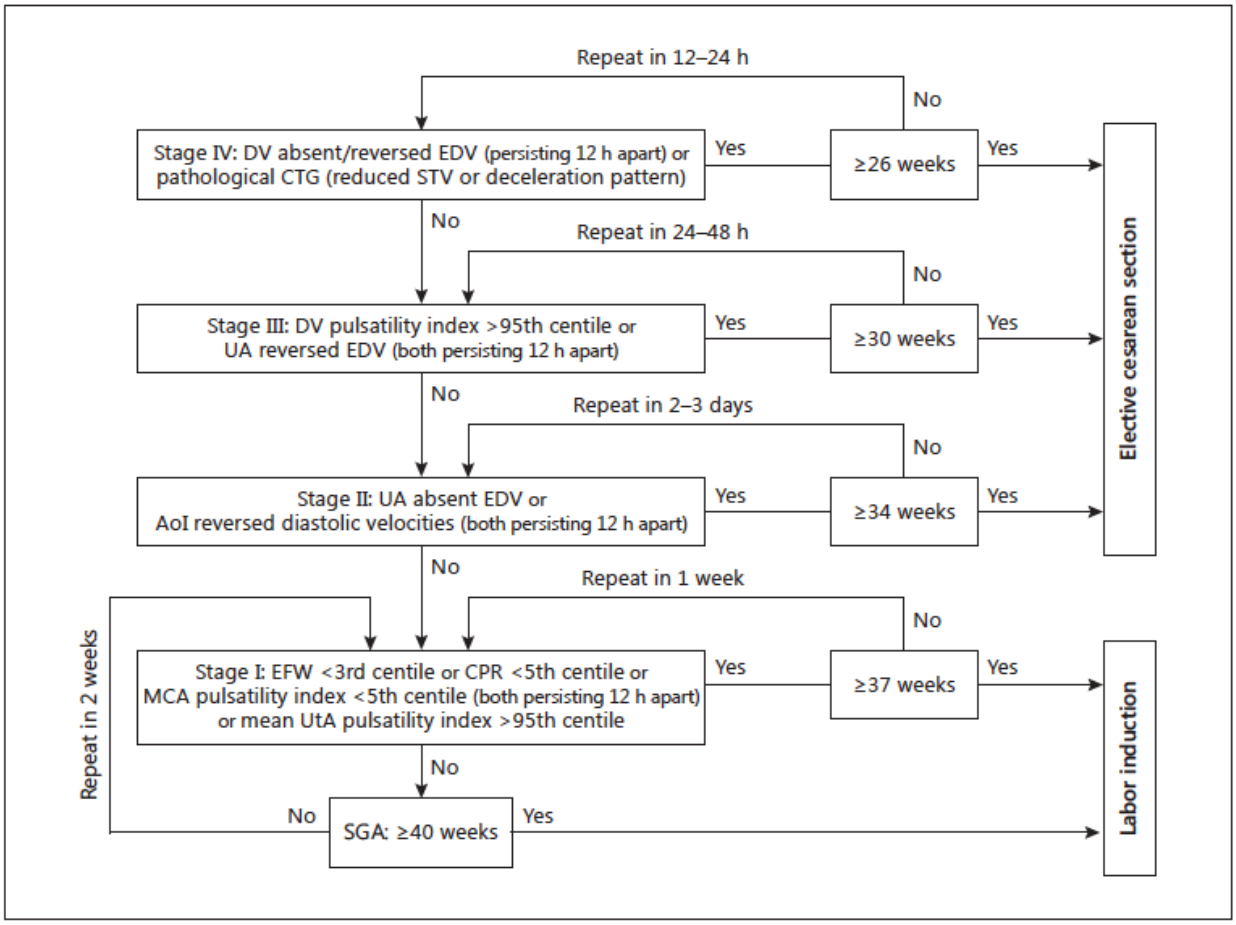
In case of a DV Doppler with a reversed wave, short-term variation in computerized cardiotocography <3 ms or decreased fetal heart rate, delivery by the elective cesarean section is recommended, depending on the availability of NICUs.

Parents should receive counseling according to the data of viability without sequelae according to the gestational age and their opinion should be taken into consideration in the delivery decision (5).

Fetal monitoring should begin between 24 and 26 weeks and should preferably be performed by combining the available tests (Doppler, fetal biophysical profile, and cardiotocography) to improve the prediction of acidosis and fetal death (7).

The prenatal use of corticosteroids should occur between 24 and 34 weeks, preferably in the week preceding the scheduled date for delivery, to accelerate fetal lung development and to reduce the risk of intracranial hemorrhage (8). However, shortly after the use of corticosteroids, the Doppler indices may present an improvement that is only transitory. For deliveries before 32 weeks, the use of magnesium sulfate is recommended for neuroprotection (8), Table 1.

Table 1: Management of FGR fetuses according to gestational age and doppler anomalies



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CHAPTER 10 PERINATAL COMPLICATIONS AND LONG-TERM NEURODEVELOPMENTAL OUTCOME OF INFANTS WITH FETAL GROWTH RESTRICTION

Neonates who are born with FGR have different types of short-term and long-term issues making them vulnerable to mortality and morbidity, both immediately and also on long- term follow-up. For these reasons these neonates needs to be followed up for delayed onset of neurological problem so that early intervention can be started on both neurological and physical aspect and lead to better outcome.

CHAPTER *10.1 Short-term complications of FGR neonates*

These infants could face many problems soon after birth. Severely affected FGR infants, subjected to oxygen and nutrients deprivation, may have difficult cardiopulmonary transition with perinatal asphyxia, meconium aspiration or persistent pulmonary hypertension (PPHN). Immediate neonatal com- plications include hypothermia, hypoglycaemia, hyperglycaemia, hypocalcaemia, polycythaemia, jaundice, feeding difficulties, feed intolerance, necrotizing enterocolitis, late onset sepsis and pulmonary haemorrhage (1).

Perinatal mortality is high in these neonates as compared with their AGA counterpart. This is seen because of adverse effect prolonged intrauterine hypoxia, birth asphyxia, sudden sentinel obstetrics events, including abruption, cord prolapse and associated congenital anomalies seen in this group (2,3).

Prevention of perinatal asphyxia includes regular antenatal and intrapartum monitoring, regular fetal growth monitoring by ultrasound, conducting delivery at appropriate time and early identification of complications with prompt referral and efficient neonatal resuscitation. It has been showed that he rate of score Apgar<7 at 5min of life was significantly higher in SGA infants when compared with AGA (RR = 2.0; 95% CI 1⁄4 1.9– 2.1) (4).

Katz et al. in a pooled analysis of 20 cohorts from developing population showed that in comparison with term AGA infants, the RR for neonatal mortality was 1.83 (95% CI 1.34–2.50) and post- neonatal mortality RR was 1.90 (1.32–2.73) for SGA infants. The risk of neonatal mortality was maximum in babies who were both preterm and SGA in comparison to babies who were either SGA or preterm alone (15.42; 9.11–26.12) (5).

Hypoglycaemia is the results of decreased glycogen stores, gluconeogenesis, increased sensitivity to insulin, decreased adipose tissue and decreased ability to oxidize free fatty acids and triglycerides effectively. Hypoglycaemia could also be due to asphyxia, polycythaemia or hypothermia. For these reasons, FGR neonates need careful sugar monitoring during the first days of life with early feeding after birth with monitoring of sign and symptoms of hypoglycaemia (1,6).

Hyperglycaemia is also seen sometimes in these FGR infants secondary to low insulin secretion rate, excessive exogenous glucose delivery and increased catecholamine and glucagon effects (6). Management includes regular monitoring of sugar level and avoiding too much glucose infusion (7).

Another common short-term complication is hypothermia. Hypothermia could be due to multiple causes, which includes relatively large body surface area, decreased body and subcutaneous tissue fat, impaired thermoregulation and catecholamine depletion. In addition, simultaneous occurrence of either hypoxia or hypoglycaemia can interfere with heat production (8).

Polycythaemia is defined as venous haematocrit more than 65%. Polycythaemia and leukoneutropenia in FGR infants is due to increased synthesis of erythropoietin secondary to chronic

intrauterine hypoxia (9,10). These FGR infants should be monitored for haematocrit at 2, 12 and 24 h after birth. If the infant is symptomatic, polycythaemia can be managed with partial volume exchange and fluid supplementation (11,12).

Chronic hypoxia in FGR infants could also cause PPHN, who may lead to remodelling of pulmonary vasculature, with extension of muscularis layer of blood vessels to intra-acinar arteries. This PPHN could also be secondary to hypocalcaemia, polycythaemias, hypoglycaemia or infections, seen in them. Management of PPHN includes avoiding hypoxia and hyperoxia, normalization of metabolic milieu, cardiovascular support, pulmonary vasodilator and mechanical ventilation (13,14).

Meconium aspiration syndrome (MAS) is seen in these FGR infants because of chronic hypoxia leading to meconium-stained liquor (MSL) and aspiration. It can occur at different stages, mild to severe MAS requiring ventilation. Management includes intrapartum fetal monitoring and early detection of MSL. Treatment involves adequate ventilation with prevention of hypoxia, adequate lung recruitment and management of PPHN (15)

Feed intolerance and necrotizing enterocolitis (NEC) is seen frequently in these FGR neonates (16). NEC is caused by decreased intestinal perfusion due to shunting of blood in response to hypoxia to vital organs, including heart, brain and adrenals, focal ischemia and hypoperistalsis (17). The incidence of NEC is increased further in FGR infants with absent or reversed end diastolic flow in the umbilical artery Doppler's (18). Management includes avoiding rapid increase in feeds, cautious enteral feeding, minimal enteral nutrition and preferable only breast milk (19).

Neurobehavioural abnormalities are also seen in this group of infants. In a study conducted by Padidela et al. who evaluated the neurobehaviour of term appropriate for gestational and SGA babies during the first two weeks of life using Brazelton neurobehavioural assessment scale reported that the behaviour performance of SGA babies on day 3, compared with AGA babies, was lower in all the clusters except orientation where they performed much better. The percentage

improvement of scores in SGA babies was higher than in AGA babies and by day 14, SGA babies were scoring higher than AGA babies in orientation, autonomic stability and regulation of state (20).

CHAPTER *10.2 Long-term neurodevelopmental outcome*

FGR infants have high probability of having subtle cognitive and neurodevelopmental abnormalities when compared with their AGA counterparts of same gestational age. The neurodevelopmental outcome of FGR infants depends upon the type of FGR, perinatal events like maternal hypertension (21), Doppler abnormalities (22,23), and perinatal asphyxia and also on the postnatal course like hypoglycaemia, neonatal sepsis, meningitis, hypoxic-ischemic encephalopathy and NEC (24).

The most common neurodevelopmental anomalies seen in FGR fetuses are:

- Lower scores on cognitive testing
- School difficulties or requirement of special education
- Gross motor and minor neurologic dysfunction
- Behavioural problems (attention deficit hyperactivity syndrome)
- Growth failure
- Reduced strength and work capacity
- Cerebral Palsy
- Low social competence
- Poor academic performance
- Lower Intelligence
- Poor perceptual performance

Martorell et al. in their systematic review of 12 studies reported that FGR infants, male and female, performed poorly on tests of strength and hence could apply approximately 2–3 kg less force to a hand grip dynamometer and had lower work capacity in comparison to AGA group (25).

In a study from India, cohort of 161 low birth weights (weight <2000 g at birth) were followed-up from birth till 18 years of age. The authors reported that among the enrolled infants SGA subjects had the lowest IQs (percentile 35.5) although within the normal range for age. SGA infants were also poor in visuo-motor perception, motor incompetence, reading and mathematics learning [26].

The adverse effects of FGR on brain structure have a variety of consequences for function. FGR infants born preterm and assessed at term equivalent age demonstrate functional deficits in neurobehavioral score for attention and responsivity, compared to appropriately grown preterm infants, with cerebral cortex grey matter volume correlated to attention–interaction score (27). At 7 months of age, FGR infants perform more poorly on a visual recognition memory task than age-matched appropriately grown infants (28). Preterm FGR infants followed-up at 1, 2 and 3 years of age showed deficits in developmental and behavioural outcomes, compared to preterm age-matched appropriately grown infants, but it is interesting to note that preterm FGR infants were not different from birthweight matched controls (that is, infants who were born at an earlier gestation but were not growth restricted) (29) Leitner et al. performed a longitudinal study from birth to 9–10 years in children born with late-onset FGR with evidence of brain sparing. This study showed that FGR children have a complex set of neurodevelopmental deficits compared to age-matched appropriately grown children (30). While suboptimal cognitive performance (IQ<85) was apparent in 15% of FGR children, they were also more likely to have specific learning disabilities such as reduced memory performance and visuomotor functions, attention and behavioural deficits (30). Where brain sparing (CPR <5th centile) was apparent, IQ at 5 years of age was 9 points lower compared to children with a normal CPR (31). Multiple follow-up studies of FGR infants into school-

age childhood find deficits in gross and fine motors kills, cognition, memory and academic ability, as well as neuropsychological dysfunctions encompassing poor attention, hyperactivity and altered mood (33-36).

It is apparent from the literature that determining the neurodevelopmental consequences of FGR is complicated by the severity of FGR, early or late onset, and the gestational age at delivery (37). Early-onset severe FGR is considered high risk for deficits in outcome, and indeed at school age, severe FGR children perform worse on assessment tasks for cognition, motor function, behaviour and educational achievements than children who had mild to moderate FGR, or preterm appropriately grown children (38) Preterm birthis likely to be an exacerbating factor when describing the neurological outcomes associated with FGR, and Yanney & Marlow [39] suggest that preterm birth over-rides the effects of FGR *per se.*

It has also been shown that serious neurodevelopmental consequences are more prevalent in FGR infants who demonstrate perinatal acidosis (40), suggesting that a secondary acute compromise has profound additive adverse effects in fetuses that have experienced chronic antenatal hypoxia.

A number of studies have analysed results based on the child's gender, where sex differences may influence neurodevelopmental outcomes for FGR infants. Parkinson and colleagues reported that poor school achievement and behavioural problems were more frequently observed in boys with early-onset growth restriction (41). This is supported by another study showing that FGR boys born very preterm (24–29weeks) were at the greatest risk of cognitive impairment examined at school age, compared to FGR preterm girls and appropriately grown preterm offspring (42).

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CHAPTER 11 STUDY 4:

Motor and neurodevelopmental outcome of infants with intrauterine growth restriction: case-control study

INTRODUCTION

FGR, is a major public health problem, and it is the second leading cause of perinatal mortality and morbidity worldwide, only second to preterm delivery (1,2). FGR is estimated to occur in 5% to 7% of all pregnancies.

It is important to separate between infants who are small for gestational age (SGA) and those who have experienced true FGR, which is generally due to placental insufficiency and is associated with an abnormal Doppler velocimetry on fetal and maternal ultrasound (3).

Approximately 5% to 10% of all pregnancies complicated by FGR result in stillbirth or neonatal death (4), and impaired fetal growth is responsible for at least 25% of all stillbirths (5). Placentally restricted fetuses are chronically hypoxemic and hypoglycemic and have increased blood lactate concentrations (4). Most infants with FGR show an increased postnatal growth velocity with catch-up growth by 2 to 3 years (6). However, because infants with FGR have feeding problems and decreased nutritional stores, approximately 10% remain susceptible to sustained growth delay (7).

It has been established that the effects of been born IUGR continue also beyond the neonatal period and the literature had widely investigated the long-term consequences of being born FGR on health and physical well-being.

Although several follow-up studies showed neurodevelopmental delay in children with FGR, these studies have not been systematically reviewed and the information, such as the definition of FGR, are often discordant between the studies and has not been adequately assessed.

The aim of this study was to prospectively evaluate the neurodevelopmental outcomes, particularly the neuro-motor assessment, in a cohort of FGR newborn at 6 and 12 months corrected age using the Bayley Scales of Infant and Toddler Development (3rd edition) (Bayley-III edition) and to compare them to a cohort of SGA infants and appropriate-for-the-gestational age (AGA) infants.

METHODS

Study design and participants

We performed a single-centre longitudinal prospective case-control study between November 2016 and October 2019. The study protocol was approved by the regional ethics committee. Patients included in the study signed a general consent form for the use of their data for scientific purposes. Inclusion criteria were: singleton pregnancy morphologically normal, attending their routine scheduled ultrasound examination between 19 and 24 weeks of gestation and between 29 and 32 weeks of gestation, maternal age >18 years old, newborn infants with intrauterine diagnosis of FGR, newborn infants SGA and newborn infants AGA. Pregnancies complicated by fetal abnormality, maternal medical disorders, aneuploidy or infection were excluded from the analysis.

In the first pregnancy-trimester, the measure of crown–rump length (CRL) was used for dating pregnancies according to the NICE (National Institute for Health and Clinical Excellence) guidelines (8).

At the time of 11–14 weeks of pregnancy, PAPP-A levels were measured as first-trimester combined screening test for Down syndrome. Both at the time of routine ultrasonography at 11–14 weeks and

of routine anomaly abdominal ultrasonography at 19–23 weeks of pregnancy, uterine artery (UtA) Doppler indices were evaluated; pulsatility index (PI) of the left and the right UtA was averaged to obtain mean PI, which was plotted against a published reference range (9). During the third pregnancy trimester, at 29–32 weeks, an ultrasonographic scan was done in all the patients to evaluate fetus growth and fetal doppler assessment.

At the first study visit, baseline maternal characteristics, including age, ethnic origin, and body mass index (BMI), parity and smoking were recorded. The maternal and neonatal outcomes of each pregnancy were collected. Delivery or follow-up scans were arranged as appropriate for any suboptimal assessments.

Gestational complications were defined with standardized criteria: pregnancy induced hypertension (PIH), detecting after 20 gestation weeks a blood pressure persistently over 140/90 mmHg in a woman with previously normal pressure values; preeclampsia, in case of gestational hypertension and concomitant proteinuria (>300 mg/24 h); preterm birth, indicating a delivery before the completion of 37 gestation weeks; SGA, in case of an infant with birth weight less than the 10th centile for gestational age with normal fetal and maternal Doppler assessment; and IUGR, according to consensus-based definitions for early and late IUGR, Delphi procedure (10).

Neurodevelopmental assessment

Children and their families were invited to take part in a follow-up assessment with Bayley Scales of Infant and Toddler Development (3rd edition)(Bayley-III) at 6 months and at 12 months corrected age.

The Bayley-III generates scores for 3 composite indices (Cognitive, Language, Motor) and 5 subtests (Cognitive, Expressive Communication, Receptive Communication, Fine Motor, Gross Motor). motion and balance) subtests. The Bayley Scales have index mean scores of 100 (SD ± 15). In the

present study, an index composite score of < 70 (>2 SD below the mean) is defined to indicate severe impairment, while an index composite score of 70–84 (>1 SD below the mean) is defined to indicate mild impairment. Index composite scores ≥ 85 are defined here to indicate normal development. The Italian validated translation of the administration manual was used (11).

Statistical analysis

The Kolmogorov–Smirnov test of normality was used for assessing the distribution of data, which were expressed as mean (SD), or median and interquartile range as appropriate. Categorical variables were described as number (%). The correlations between continuous variables were evaluated by Pearson coefficient or by Spearman rho and those between categorical variables were evaluated by Pearson x2 test. Continuous variables were compared by Mann–Whitney and independent t-tests.

Mean UtA Doppler PI, estimated fetal weight (EFW) centiles, and z-scores were calculated by using appropriate previously described reference ranges (9). Mean UtA Doppler PI was corrected for gestational age; multiple of medians were calculated by using the reference ranges extracted from the published centiles (9). $P < 0.05$ was considered statistically significant. Appropriate statistical software (SPSS 20.0; SPSS Inc, Chicago, IL) was employed for the statistical data analysis.

RESULTS

Demographic, pregnancy characteristics and postnatal outcomes of the three groups of patients are presented in Tables 1, Table 2 and Table 3.

There was no statistically significant difference in the baseline data within the three study groups.

Overall, 81 newborn had complete follow-up, as required for being eligible for the study analysis; within this population, 27 (33,3%) were FGR, 27 (33,3%) were SGA, and 27 (33,3%) were AGA.

Comparing IUGR group to AGA group, pregnant women presented significantly lower first-trimester PAPP-A level, and significantly higher first-trimester and mid-pregnancy mean UtA-PIs. Moreover, the IUGR group had a significantly lower gestational age (GA) at the time of delivery and a significantly higher admission rate to neonatal intensive care unit (NICU) compared to the AGA group (Table 1).

Comparing IUGR group to SGA group, pregnant women presented significantly higher first-trimester and mid-pregnancy mean UtA-PIs, significantly lower GA and birth weight (BW) at the time of delivery and a significantly higher admission rate to NICU compared to the AGA group (Table 2).

A statistically significant difference was not observed in the first trimester levels of PAPP-A and first trimester and mid-pregnancy mean UtA Doppler PI between SGA and AGA group. A statistically significant lower GA and BW was observed, however no difference has been observed in the NICU admission rate (Table 3).

The composite indices (Cognitive, Language, Motor) were significantly lower in FGR group compared to AGA group both at 6 and 12 months evaluation (Table 4). The composite indices (Cognitive, Language, Motor) were significantly lower in FGR group compared to SGA group at 6 month evaluation. However, at 12 months evaluation only the Motor composite indices was significantly lower in IUGR group, Table 5.

Comparing the AGA and SGA groups, no statistically significant difference was found at 6 month evaluation for all the composite indices (Cognitive, Language, Motor). However, at 12 months evaluation the Motor composite indices was significantly lower in SGA group, Table 6.

Table 1. Demographic and ultrasound variables and outcome in pregnant women with IUGR and AGA newborn

	FGR (n = 27)	**AGA** (n = 27)	**P value**
Demographics			
Maternal age, (years, median, IQR)	29,6 (27,5-32,5)	31,7 (29,0-35,0)	0,074
Nulliparous (n, %)	22 (81,5)	22 (81,5)	1,000
BMI (kg/m^2, mediana, IQR)	22,9 (21,0 – 25,0)	23,2 (21,6-24,5)	0,757
Race (n, %) ▪ Caucasian ▪ Afro-Caribbean Asian	22 (81,5) 4 (14,8) 1 (3,7)	24 (88,9) 2 (7,4) 1 (3,7)	0,686
Previous early miscarriage (n, %)	7 (25,9)	4 (14,8)	0,311
Smoking (n, %)	5 (18,5)	4 (14,8)	0,751
1st and 2nd trimester variables			
PAPP-A (MoM, mediana, IQR)	0,81 (0,48-1,11)	1,17 (0,66-1,83)	<0,05
BhCG (MoM, mediana, IQR)	1,04 (0,67-1,46)	1,23 (0,93-1,58)	0,174
Mean UtA PI 1st trimester (median, SD)	2,01 (±0,50)	1,52 (±0,69)	<0,05
Mean UtA PI 2nd trimester (median, SD)	1,65 (±0,55)	0,98 (±0,24)	<0,05
Scan assessment during the 3rd trimester of pregnancy			
Gestational age 3rd trimester scan (median, SD)	33,4 (±1,3)	32,3 (±2,0)	0,810
EFW (g, mean, SD)	1495 (±205)	1909 (±351)	<0,05
EFW centile (mean, SD)	5,7 (±3,9)	49,9 (±27,5)	<0,05
Pregnancy and perinatal outcome			
Gestational age delivery (median, IQR)	36,9 (±1,4)	39,0 (±1,4)	<0,05
BW (mean, SD)	2192 (±322)	3319 (±404)	<0,05
BW centile (mean, SD)	4,4 (±3,3)	49,1 (±25,3)	<0,05
NICU admission (n, %)	10 (37,0)	2 (7,4)	<0,05

Data are shown as median (interquartile range), mean (standard deviation) or number (%).

Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; birth weight: BW; neonatal intensive care unit: NICU; fetal growth restriction: FGR; appropriate for gestational age: AGA; Uterine artery: UtA; Pulsatility index: PI

Table 2. Demographic and ultrasound variables and outcome in pregnant women with FGR and SGA newborn

	FGR (n = 27)	**SGA** (n = 27)	**P value**
Demographics			
Maternal age, (years, median, IQR)	29,6 (27,5-32,5)	29,1 (26,5-32,0)	0,658
Nulliparous (n, %)	22 (81,5)	20 (74,1)	0,513
BMI (kg/m^2, mediana, IQR)	22,9 (21,0 – 25,0)	22,5 (20,0-24,5)	0,596
Race (n, %) ▪ Caucasian ▪ Afro-Caribbean ▪ Asian	22 (81,5) 4 (14,8) 1 (3,7)	25 (92,6) 1 (3,7) 1 (3,7)	0,369
Previous early miscarriage (n, %)	7 (25,9)	6 (22,2)	0,750
Smoking (n, %)	5 (18,5)	5 (18,5)	1,000
1st and 2nd trimester variables			
PAPP-A (MoM, mediana, IQR)	0,81 (0,48-1,11)	0,87 (0,60-0,98)	0,611
BhCG (MoM, mediana, IQR)	1,04 (0,67-1,46)	1,05 (0,57-1,37)	0,931
Mean UtA PI 1st trimester (median, SD)	2,01 (±0,50)	1,49 (±0,49)	<0,05
Mean UtA PI 2nd trimester (median, SD)	1,65 (±0,55)	0,98 (±0,30)	<0,05
Scan assessment during the 3rd trimester of pregnancy			
Gestational age 3rd trimester scan (median, SD)	33,4 (±1,3)	32,9 (±0,97)	0,068
EFW (g, mean, SD)	1495 (±205)	1626(±203)	<0,05
EFW centile (mean, SD)	5,7 (±3,9)	6,7 (±2,9)	0,321
Pregnancy and perinatal outcome			
Gestational age delivery (median, IQR)	36,9 (±1,4)	37,9 (±1,7)	<0,05
BW (mean, SD)	2192 (±322)	2331 (±303)	0,109
BW centile (mean, SD)	4,4 (±3,3)	4,5 (±2,9)	0,837
NICU admission (n, %)	10 (37,0)	4 (14,8)	0,062

Data are shown as median (interquartile range), mean (standard deviation) or number (%).

Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; birth weight: BW; neonatal intensive care unit: NICU; fetal growth restriction: FGR; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

Table 3. Demographic and ultrasound variables and outcome in pregnant women with AGA and SGA newborn

	AGA (n = 27)	**SGA** (n = 27)	**P value**
Demographics			
Maternal age, (years, median, IQR)	31,7 (29,0- 35,0)	29,1 (26,5-32,0)	0,121
Nulliparous (n, %)	22 (81,5)	20 (74,1)	0,513
BMI (kg/m^2, mediana, IQR)	23,2 (21,6-24,5)	22,5 (20,0-24,5)	0,361
Race (n, %) ▪ Caucasian ▪ Afro-Caribbean ▪ Asian	24 (88,9) 2 (7,4) 1 (3,7)	25 (92,6) 1 (3,7) 1 (3,7)	0,838
Previous early miscarriage (n, %)	4 (14,8)	6 (22,2)	0,484
Smoking (n, %)	4 (14,8)	5 (18,5)	0,715
1st and 2nd trimester variables			
PAPP-A (MoM, mediana, IQR)	1,17 (0,66-1,83)	0,87 (0,60-0,98)	0,098
BhCG (MoM, mediana, IQR)	1,23 (0,93-1,58)	1,05 (0,57-1,37)	0,221
Mean UtA PI 1st trimester (median, SD)	1,52 (±0,69)	1,49 (±0,49)	0,899
Mean UtA PI 2nd trimester (median, SD)	0,98 (±0,24)	0,98 (±0,30)	0,994
Scan assessment during the 3rd trimester of pregnancy			
Gestational age 3rd trimester scan (median, SD)	32,3 (±2,0)	32,9 (±0,97)	0,116
EFW (g, mean, SD)	1909 (±351)	1626(±203)	<0,05
EFW centile (mean, SD)	49,9 (±27,5)	6,7 (±2,9)	<0,05
Pregnancy and perinatal outcome			
Gestational age delivery (median, IQR)	39,0 (±1,4)	37,9 (±1,7)	<0,05
BW (mean, SD)	3319 (±404)	2331 (±303)	<0,05
BW centile (mean, SD)	49,1 (±25,3)	4,5 (±2,9)	<0,05
NICU admission (n, %)	2 (7,4)	4 (14,8)	0,386

Data are shown as median (interquartile range), mean (standard deviation) or number (%).

Body Mass Index: BMI; pregnancy-associated plasma protein A: PAPP-A; beta human chorionic gonadotropin: BhCG; estimated fetal weight: EWF; birth weight: BW; neonatal intensive care unit: NICU; appropriate for gestational age: AGA; small for gestational age: SGA; Uterine artery: UtA; Pulsatility index: PI

Table 4. The Bayley-III generates scores for 3 composite indices (Cognitive, Language, Motor) at 6 and 12 months in FGR and AGA newborns.

	IUGR (n = 27)	**AGA** (n = 27)	**P value**
Bayley score 6 months			
Cognitive indices (mean, SD)	80,4 (± 6,7)	88,1 (±4,7)	<0.05
Motor indices (mean, SD)	79,6 (±7,2)	86,8 (±5,1)	<0,05
Language indices (mean, SD)	81,2 (±6,6)	87,1 (± 5,2)	<0,05
Bayley score 12 months			
Cognitive indices (mean, SD)	83,4 (± 5,6)	89,6 (± 3,9)	<0,05
Motor indices (mean, SD)	80,7 (± 7,0)	89,0 (± 3,6)	<0.05
Language indices (mean, SD)	83,4 (± 6,4)	88,5 (± 6,7)	<0,05

Data are shown as mean (standard deviation).

Intrauterine growth restriction: IUGR; appropriate for gestational age: AGA

Table 5. The Bayley-III generates scores for 3 composite indices (Cognitive, Language, Motor) at 6 and 12 months in FGR and SGA newborns.

	FGR (n = 27)	**SGA** (n = 27)	**P value**
Bayley score 6 months			
Cognitive indices (mean, SD)	80,4 (± 6,7)	85,6 (±6,4)	<0,05
Motor indices (mean, SD)	79,6 (±7,2)	84,3 (±5,1)	<0,05
Language indices (mean, SD)	81,2 (±6,6)	85,4 (±5,9)	<0,05
Bayley score 12 months			
Cognitive indices (mean, SD)	83,4 (± 5,6)	85,4 (±5,8)	0,206
Motor indices (mean, SD)	80,7 (± 7,0)	85,6 (±5,1)	<0,05
Language indices (mean, SD)	83,4 (± 6,4)	85,9 (±5,1)	0,124

Data are shown as mean (standard deviation).

Fetal growth restriction: FGR; small for gestational age: SGA

Table 6. The Bayley-III generates scores for 3 composite indices (Cognitive, Language, Motor) at 6 and 12 months in AGA and SGA newborns.

	AGA (n = 27)	**SGA** (n = 27)	**P value**
Bayley score 6 months			
Cognitive indices (mean, SD)	88,1 (±4,7)	85,6 (±6,4)	0,106
Motor indices (mean, SD)	86,8 (±5,1)	84,3 (±5,1)	0,075
Language indices (mean, SD)	87,1 (± 5,2)	85,4 (±5,9)	0,265
Bayley score 12 months			
Cognitive indices (mean, SD)	89,6 (± 3,9)	85,4 (±5,8)	0,089
Motor indices (mean, SD)	89,0 (± 3,6)	85,6 (±5,1)	<0,05
Language indices (mean, SD)	88,5 (± 6,7)	85,9 (±5,1)	0,061

Data are shown as mean (standard deviation).

Small for gestational age: SGA; appropriate for gestational age: AGA

DISCUSSION

Main findings

This study demonstrate that the mean score for the Cognitive, Language and Motor indices were significantly lower in FGR group compared both to AGA group and SGA group at 6 months evaluation. However, at 12 months examination, while all the indices remained significantly lower in IUGR group compared to AGA group, in the comparison with the SGA group only the motor score remained significantly lower in the FGR group. Moreover, comparing the AGA and SGA groups, no statistically significant difference was found at 6 month evaluation for all the composite indices (Cognitive, Language, Motor). However, at 12 months evaluation the Motor composite indices was significantly lower in SGA group.

Interpretation

The findings of our study confirm previous observations that FGR infants are at increased risk for adverse neurodevelopmental outcome compared to AGA and SGA infants (12,13).

According to the existing literature four studies examined neurodevelopmental outcome in children with FGR between 6 months and 1 year of age. Two of these study defined IUGR only according to the low birth weight or fetal abdominal circumference below the 5^{Th} centile, without references to fetal and maternal doppler assessment (14,15). The first study performed by Fernandez-Carrocera et al. (14), showed that infants with FGR had higher prevalence of neuromotor and neurologic abnormalities than controls at 1 year, although most of the abnormalities were mild. FGR was the best predictor marker of neurological impairment at 1 year. Moreover, they also showed that infants with FGR scored significantly lower than controls on the Bayley Scales of Infant Development, version II (Bayley-II), although both groups scored within 1 SD of the mean (14). In the second study, Roth et al (15), compared at 1 year of age neurological outcome between FGR

and SGA infants. They defined FGR as a change in fetal abdominal circumference >1.5 SD between the first and last scan, whereas SGA was indicated when fetal abdominal circumference changed <1.5 SD, and found no significant differences in neurodevelopment between these groups. However, approximately 1/3 of FGR and SGA infants had some neurological damage.

The other two studies conducted with children between 6 months and 1 year of age, who had prenatal diagnosis of FGR, included abnormal Doppler parameters in their definition (16,17). In the first study, preterm infants with asymmetric FGR had significantly lower neurobehavioral scores on the habituation, motor system, social-interactive, and attention subscales of the Neonatal Behavioral Assessment Scale at 40 weeks when compared with both controls and infants with symmetric FGR. Asymmetric fetal growth restriction, mainly due to the "brain-sparing" effect, occurs late in pregnancy, and infants show weight reduction but a less marked length reduction. In the second study, Padilla et al. (17) compared preterm children with and without FGR using the Hammersmith Infant Neurologic Examination and the Bayley-II at 1 year of age, and found no significant differences between the groups in neurodevelopmental performance. Thus, three of the four studies assessing neurodevelopment between 6 months and 1 year indicate that these children are at higher risk for neurodevelopmental delay.

Accumulating evidence suggests that cerebral redistribution may be associated with increased risk of adverse neurodevelopmental outcomes (18-22). A recent systematic review suggest that cerebral redistribution in SGA fetuses may not be an entirely protective phenomenon (23). Cerebral redistribution in term SGA fetuses was found to be associated with increased risk of problems in neonatal motor and state organization, and lower communication and problem-solving scores at 2 years of age. Cerebral redistribution in preterm SGA fetuses was also found to be associated with increased risk of abnormal psychomotor development at 1 year of age. Few studies reported long-

term outcomes, and maximum follow up was 2 years (23). Longitudinal data are limited; therefore, the prognostic clinical significance of early neurological findings is uncertain.

Doppler studies investigating cerebral redistribution in fetal growth restriction suggest that an increase in frontal lobe perfusion occurs first, detected by changes in the anterior cerebral artery. This is followed by changes in the middle cerebral artery (MCA), which supplies the basal ganglia and influences motor function. As MCA changes are indicative of an advanced stage of brain sparing, it is possible that impact on cognitive function through abnormal frontal lobe perfusion has already occurred by the time that MCA changes are detected (24,25).

Although cerebral redistribution may offer neuroprotection in some, this may not completely mitigate the effects of hypoxia and it is unknown at what point following cerebral redistribution there is an increased risk of adverse neurodevelopmental sequelae.

Strengths and limitations

The first limitation is the small sample size. The small number of newborn in each group did not allow further subanalysis to be performed, particularly the analysis according the GA at birth. For this reason is not possible to exclude the impact of being born preterm on the neurodevelopmental outcomes. The second major limitation is the short follow-up period. A longer follow-up could have gave us a better neurological assessment, in particular underlining the differences between the various domains between the three study groups. However, these preliminary findings may pave the way for future studies with a larger sample size and a longer follow-up. The main strength of this study is that we classified our study population according to distinct signs of placental dysfunction including prenatal fetal and maternal Doppler parameters and analyzed the short-term outcome of FGR infants compared with children being SGA without such signs of placental insufficiency. This design seems to be advantageous compared with the majority of pediatric studies

on short and long-term outcome using a mixed population of newborns just being small or light at birth. The latter might lead to a bias by underestimating the real impact of intrauterine growth restriction on neurological outcome.

CONCLUSION

In conclusion, the current study shows that FGR newborn had a significantly lower mean score on each domains (Cognitive, Language and Motor) at 6 months compared to SGA and AGA infants. However, at 12 months examination, while all the indices remained significantly lower in FGR group compared to AGA group, in the comparison with the SGA group only the motor score remained significantly lower in the FGR group, probably due to the fetal cerebral distribution that may affect mainly the motor centers.

Further follow-up studies would be helpful to expand existing knowledge of the effects of IUGR on neurodevelopment in early childhood, but it is essential to standardize definitions, study designs, and outcome measures.

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CHAPTER 12. CONCLUSION

FGR remains a leading contributor to perinatal mortality and morbidity and metabolic syndrome in later life. Significant advances have been made in the understanding of the complex etiology and pathophysiology of FGR. This knowledge will certainly aid the clinician to optimize antepartum monitoring and time delivery of FGR infants.

It is well known that the etiology of FGR can be categorized into maternal, fetal and placental factors. In this three year project one of our research line was to evaluate the impact of some maternal condition, such as adenomyosis and endometriosis, on the incidence of FGR.

The first study, published in 2018, had the aim of evaluate maternal and fetal outcomes, in particular the incidence of FGR, in a cohort of women with endometriosis with or without the concomitant presence of diffuse or focal adenomyosis. This was a retrospective study, with a relatively small number of patients recruited, however the results were quite interesting. The results showed that the presence of diffuse adenomyosis in pregnant women with endometriosis is strongly associated with delivery of a FGR infant. Women with endometriosis and diffuse adenomyosis might be considered being at high risk of placental dysfunction and might need closer monitoring during pregnancy. These results are also potentially useful for preconception and prenatal counseling of women with both adenomyosis and endometriosis.

Since this first study showed a strong correlation between adenomyosis and FGR in women with endometriosis, the second study that we performed was to ascertain the role of each endometriotic phenotypes, in particular ovarian endometrioma (OE) and deep endometriosis (DE), as specific risk factor for developing adverse perinatal outcomes in women with endometriosis.

This retrospective study, published in 2019, aimed to investigate if perinatal and maternal outcomes, particularly with regard to prevalence of FGR infants, are different in pregnant women with OE versus those with DE without OE. This study showed, for the first time in the literature, that

that neither the presence of OE nor that of DE alone were considered relevant risk factors for placental impairment and consequently delivering FGR infants. Thus, patients affected by endometriosis should be treated during pregnancy as the general population, not needing closer monitoring.

It is well known that FGR infants have high chances of having subtle cognitive and neurodevelopmental abnormalities when compared with their AGA counterparts of same gestational age. The main focus of this three years PhD was to prospectively evaluate the neurodevelopmental outcomes, particularly the neuro-motor assessment, in a cohort of FGR newborn at 6 and 12 months corrected age using the Bayley Scales of Infant and Toddler Development (3rd edition) (Bayley-III edition) and to compare them to a cohort of SGA infants and AGA infants. Children and their families were invited to take part in a follow-up assessment with Bayley Scales of Infant and Toddler Development (3rd edition)(Bayley-III) at 6 months and at 12 months corrected age. The Bayley-III generates scores for 3 composite indices (Cognitive, Language, Motor) and 5 subtests (Cognitive, Expressive Communication, Receptive Communication, Fine Motor, Gross Motor). motion and balance) subtests. The findings of our study confirm previous observations that FGR infants are at increased risk for adverse neurodevelopmental outcome compared to AGA and SGA infants. FGR newborn had a significantly lower mean score on each domains (Cognitive, Language and Motor) at 6 months compared to SGA and AGA infants. However, at 12 months examination, while all the indices remained significantly lower in FGR group compared to AGA group, in the comparison with the SGA group only the motor score remained significantly lower in the FGR group, probably due to the fetal cerebral distribution that may affect mainly the motor centers.

Further follow-up studies, with longer follow-up, would be helpful to expand existing knowledge of the effects of FGR on neurodevelopment in early childhood, but it is essential to standardize definitions, study designs, and outcome measures.